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# SURGERY

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## Original Communications

Society of University Surgeons, St. Louis, Mo.,  
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### THE ROLE OF EPITHELIZATION AND CONTRACTURE IN THE HEALING OF THE PEPTIC ULCER

#### A PRELIMINARY REPORT

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THE question of just how chronic the peptic ulcer really is and what is the nature of its chronicity needs further consideration. It is not known, for example, whether the chronic state results from the destruction of a large amount of stomach wall with terminally slow healing or whether only a small amount of tissue is originally destroyed and an inhibiting factor or factors keep the defect open. In this preliminary report an attempt is made to evaluate the chronicity of healing of artificial gastric defects resulting from the destruction of known amounts of the various tissue layers of the stomach wall and to compare the healing of these defects both grossly and microscopically with pathology of the peptic ulcer.

#### METHOD

Known amounts of mucosa alone, muscle and serosa, and all three layers were excised from the anterior wall of the prepyloric area of the stomachs of fully anesthetized dogs. When all three layers were removed, the omentum was sutured over the remaining defect. The dogs were returned to their regular diets and killed at various intervals. The size of the resulting lesion was measured and microscopic sections cut.

#### RESULTS

Up to 4 square inches of mucosa were removed and the defects healed without showing any signs of chronicity. Contraction of the stomach

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wall occurring immediately after cutting and during healing accounted for most of the closure. A reduction in size amounting to as much as 25 per cent of the original was observed to take place as soon as the stomach was allowed to resume its natural position again in the abdominal cavity. During healing, these defects of the mucosa alone did

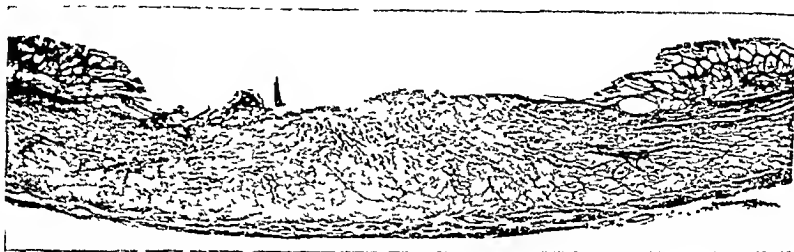


Fig. 1.—Healing of mucosal defect. The muscle is intact and over it is a layer of young fibrous tissue without surface necrosis. A thin layer of epithelium is extending from normal mucosa on either side.

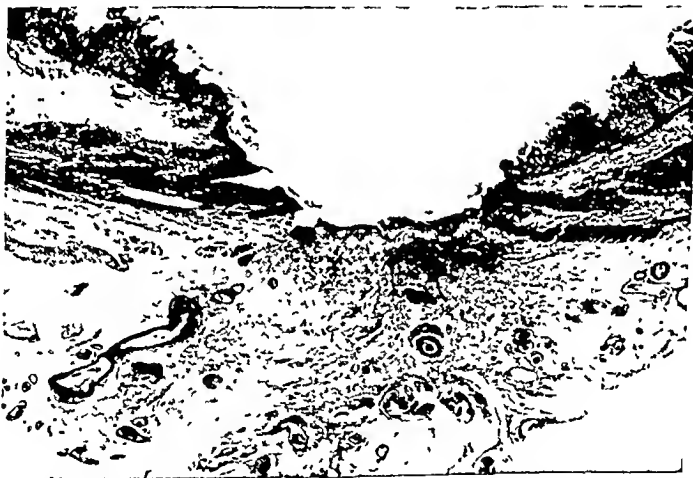


Fig. 2.—The usual anatomy of the chronic peptic ulcer. The muscles are separated by a fibrous base with surface necrosis. This fibrosis extends beyond the wall of the stomach where there are many thrombosed vessels. The epithelium is not regenerating. (After Hurst and Stewart.)



Fig. 3.—Atypical anatomy of chronicity. Muscle intact. Marked fibrosis under mucosa on either side. (After Hurst and Stewart.)

not resemble chronic peptic ulcer whatsoever. Epithelization began after the usual latent period. The cells at the edge of the defect arranged themselves in a single layer and extended across a narrow granulating base existing above intact muscle. (Fig. 1.) In distinct contrast, Hurst and Stewart<sup>1</sup> stress that 96 per cent of all chronic ulcers have destruction and replacement fibrosis of the muscle extending down to or beyond the serosa (Fig. 2). The other 4 per cent have either questionable chronicity or some degree of it because excessive fibrosis takes place between the muscularis mucosa and the muscle at the edge of the defect (Fig. 3).

Removal of 4 square inches of serosa and muscle without removal of mucosa did not result in any corresponding or smaller area of necrosis of the mucosa. Mucosal ulcerations did not take place during healing, although the underlying muscle was destroyed. The omentum spontaneously attached itself to the area where the muscle and serosa were removed, contraction reduced the size of this type of defect also, and as it grew smaller the omentum again began to separate.

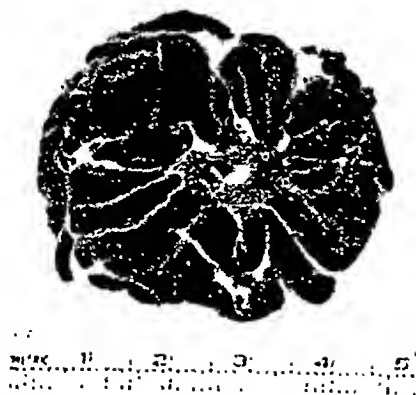


Fig. 4.—Gross appearance of the 1 inch square defect of all three layers after thirty days of healing.

When 1 square inch of all three layers of the stomach wall was destroyed, a defect resulted which after thirty days of healing was of the size of the chronic peptic ulcer or slightly larger and exactly resembled its microscopic picture (Figs. 4, 5, and 6). The muscle was separated and its base was all fibrous tissue with surface necrosis. Epithelization had begun to occur, but irregularly at one or the other edge, and was small in amount. It is of interest that the granulating bed of one of these defects was oozing blood when the animal was killed on the twenty-seventh day. Larger areas of muscle up to 4 square inches in size have also been destroyed in conjunction with a 1 square inch defect of mucosa. Destruction of this additional amount of muscle did not seem to contribute to chronicity more than the destruction of equal amounts of all three layers. In either case the ulcer was of approximately the same size after the same interval. Contraction of muscle occurred after

the larger amount was destroyed for microscopically it could be seen at the edge of the defect.

#### DISCUSSION

How long defects of various sizes of all three layers of the stomach wall will remain open and what will be the effect on their healing with

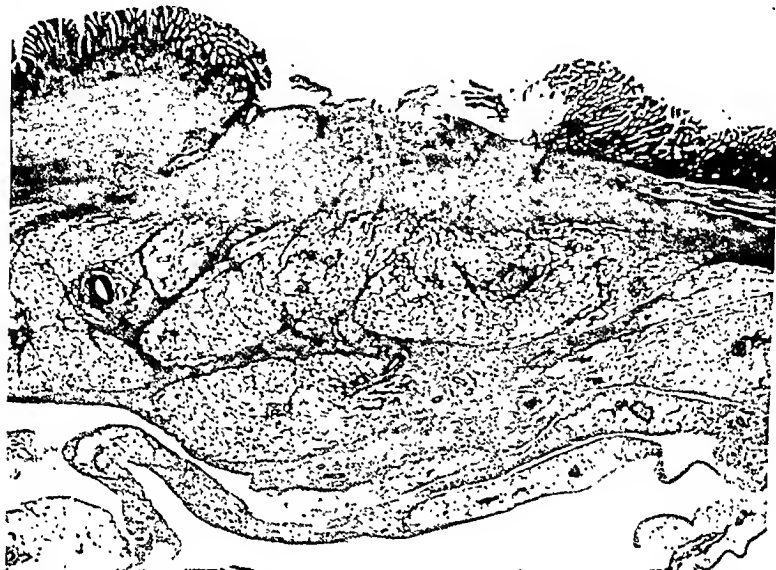


Fig. 5.—Microscopic appearance of a similar defect after twenty-seven days of healing. Muscle seen only on the left. Fibrous base with surface necrosis. Fibrosis extends beyond the stomach wall and contains many thrombosed vessels. The epithelium is not regenerating.

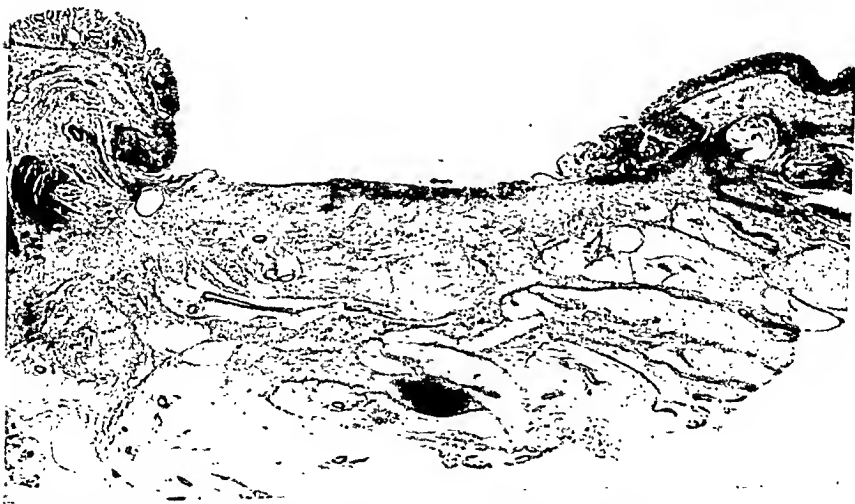


Fig. 6.—Microscopic appearance of another similar defect after thirty days of healing. Muscle seen only on the left. Epithelium regenerating somewhat on both sides. Surface necrosis not as marked.

an irregular secretion or an unusual quantity of acid and pepsin will be reported later. Certainly when mucosa and only part of the muscle were destroyed, Flood and one of us (E. L. H.)<sup>2</sup> could only temporarily delay healing although enough acid and pepsin were given over a sufficient length of time to digest the experimental animal. Only a few of these lesions perforated and the rest healed in two or three weeks. At the end of one week, however, most of them exhibited the characteristics of the chronic peptic ulcer; namely, overhanging or nonproliferating epithelial edges and fibrosis or granulations with surface necrosis replacing the muscle. To the contrary, these three layer defects with an omental patch still showed all the signs of chronicity at the end of a month, although there had been no alteration in their chemical environment during healing.

It is important to realize that the resemblance of chronicity can be duplicated in so short a period of time as a week or ten days. Duplication, then, is only significant when it continues to exist. The number of agents and methods which will produce this duplication with or without associated gastritis and multiple ulcerations are legion: surgical duodenal drainage, cinchophen poisoning, parenteral aspirin, brain tumors in the region of the basal ganglia, continuous stimulation of the vagus, avitaminosis, irregular and prolonged gastric secretion from ingestion of alcohol, caustics, irritants, and chronic histamine stimulation, upper respiratory infections, and many others. With many of these methods the animals die either from perforation or from other debilitating or toxic effects associated with the method of production soon after the ulcer is produced. Chronicity is simulated, but the animals never live long enough to find out whether the lesions are actually chronic. Usually, when the debilitating or toxic action is removed, the lesions promptly heal. Only recently with cinchophen<sup>3</sup> and chronic histamine stimulation<sup>4</sup> has there been some hope of carrying out real chronic experiments. The method herein described offers an experimental opportunity to separate and evaluate destructive action and the factors producing chronicity. Both may be related, of course.

This work further suggests that the chronicity of peptic ulcer may in many instances be caused by the destruction of larger amounts of tissue than is usually supposed or that contraction is eliminated in some way. Because perforations are pin point, because mucosal ulcerations are of small diameter when acute, and because the actual size of the chronic ulcer rarely exceeds 1.5 cm., it is generally assumed that the amount of tissue destroyed is necessarily small and some inhibiting factor keeps it open. To the contrary, evidence is presented that relatively larger amounts of tissue may be originally destroyed, and contraction brings the area down to a size consistent with the usual chronic peptic ulcer.

Clinically, the ulceration of the stomach either heals, perforates, or becomes chronic. Despite the presence of acid everywhere, the chronic

ulcer occurs largely on the lesser curvature where destruction extends into the mesentery or in the posterior wall where it extends into the pancreas or into an adherent lesser sac (76 per cent of chronic ulcers occur in these two locations), or on the anterior wall into a lapel of the liver, or into some surrounding adherent organ. The anatomical coincidence of the involvement of three layers of the stomach wall and the fixation of this point in some manner with negation of the forces of contraction forms a pattern of healing which cannot be neglected as a factor determining the chronicity of the peptic ulcer of the stomach.

#### SUMMARY

1. Contraction plays a large role in the closure of any defect in the wall of the stomach.
2. Destruction of all three layers of the wall of the stomach repaired with a patch of omentum produces during healing the gross and microscopic picture of the chronic peptic ulcer.
3. The microscopic pathology of chronic peptic ulcer can be duplicated in ten days, but this similarity is only significant when it continues to exist over a subsequent period of time.
4. After healing for thirty days, a 1 square inch defect of all three layers of the stomach wall still had the appearance of chronicity, although there had been no change in its chemical environment during healing.
5. Because of contraction, the size of the chronic peptic ulcer may misrepresent the amount of tissue which was originally destroyed; or if not, then contraction must be inactivated in some way during healing.
6. Most experimental methods of producing peptic ulcer have simply duplicated the pathologic picture of chronicity and have not yet indicated whether the lesion will continue to have this appearance over some period of time.
7. The method herein described offers an opportunity to test whether the destructive factors which produce the pathologic picture of peptic ulcer will also cause chronicity.
8. The anatomy of the chronic peptic ulcer contributes to its chronicity.

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# AUTOGENOUS CARTILAGE GRAFTS

## AN EXPERIMENTAL STUDY

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OUR knowledge concerning cartilage transplantation is in a somewhat confused state at present. This is due to reports of clinically successful transplantations not only of autogenous grafts, but also of homogenous grafts, and even of so-called "refrigerated isografts." This confusion is undoubtedly abetted by the fact that cartilage is an avascular tissue which probably lives largely by lymph diffusion, and because it requires so little for sustenance, degenerative changes take place quite slowly. Hence clinical observations may be of questionable value as the period of observation may be too short to determine the ultimate fate of the transplant.

### CLINICAL EVIDENCE

*Autogenous.*—Clinically there is a well-founded belief that autogenous rib cartilage grafts live when transplanted to almost any location and that they neither increase nor decrease in size. It is also believed that they change little microscopically, other than undergoing that calcification which normally occurs. There are many reports in the literature concerning their successful clinical use.

*Living Homogenous.*—Living homogenous grafts have not been extensively used clinically, but because of the great difficulties encountered in satisfactorily restoring the ear, Gillies<sup>1</sup> in 1937 attempted and reported the successful transplantation of maternal auricular cartilage to the son, in the correction of traumatic and congenital microtia. Following this report, others have reported on this procedure as being practicable. J. B. Brown<sup>2</sup> in 1940 reported clinically successful cases of rib cartilage transplants from father and mother to sons, in the correction of traumatic deformities of the nose and orbit.

*Dead Cartilage.*—Dead preserved transplants of both animal and human cartilage were used rather extensively two decades and more ago. These were employed mainly in the correction of saddle noses. The procedure was gradually discarded because it was believed that these inserts were absorbed.

Within the past ten years there has been a revival of the use of these so-called preserved homografts. These are not in the strict sense of the word grafts, for I do not believe that even their staunchest advocates

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would consider them to be living tissue. They are dead cartilage removed from cadavers and preserved in one way or another.

In 1938 O'Connor and Pierce<sup>3</sup> reported on what they call "refrigerated cartilage isografts." Rib cartilage from a cadaver is preserved under sterile precautions in a solution of one part 1:1,000 aqueous merthiolate to four parts of normal saline solution in the refrigerator. They report the use of cartilage stored for as long as two years. Of 375 transplants done, 6 became infected, of these only 1 was totally lost. They state that after five years the transplants still maintained their original size and identity.

In 1940 Kirkham<sup>4</sup> reported the successful use of cadaver auricular cartilage, preserved in the same manner, in reconstruction of subtotal losses of the ear.

From these clinical reports one would conclude that either living autogenous or homogenous cartilage can be successfully transplanted, and that dead homogenous cartilage will persist as a foreign body in the tissues for a long period of time without loss of size.

#### EXPERIMENTAL EVIDENCE

*Autogenous.*—The experimental data available would indicate that the clinical belief concerning autogenous cartilage grafts is correct. In 1917 Davis<sup>5</sup> found that cartilage grafts remain of original size when transplanted subcutaneously in dogs with one end of the graft in contact with bone, while similar experiments with bone grafts show that they are gradually completely absorbed.

Loeb<sup>6</sup> in 1926 reported that of the cartilage grafts from various sources autografts are tolerated with less reaction and with less eventual loss of substance.

In 1938, Peer<sup>7</sup> showed that in man autogenous cartilage grafts retained their normal structure and were not absorbed or invaded. This conclusion was based on microscopic examination of segments of costal cartilage buried beneath the chest skin and removed at intervals of six months to six years.

In 1940, Kirkham<sup>4</sup> showed microscopic sections of autogenous rib cartilage which had been stored in the abdominal subcutaneous tissues of a patient for ten years and had not lost its cartilaginous characteristics.

*Homogenous Grafts.*—Experimental data concerning homogenous living transplants of cartilage are quite scarce. Loeb and Siebert<sup>8</sup> report that there is greater tissue reaction to, and more eventual absorption of, homogenous cartilage grafts than of autogenous.

*Dead Homogenous Implants.*—The experimental work concerning dead homogenous implants is also rather meager. Peer<sup>7</sup> reported that



he had buried cadaver rib cartilage preserved in alcohol under the skin of patients and then removed the implants at intervals of seven days up to two years. Histologic examination of the removed specimens showed that a rather intense inflammatory reaction takes place at once. A thick connective tissue capsule forms about the implant, walling it off. This reaction lasts about a month and then largely disappears. The cartilage then acts as an inert but tolerated foreign body up until about nine months. From then on there is progressive invasion of the cartilage by fibrous tissue and partial absorption takes place.

Kirkham's<sup>4</sup> findings using the ear cartilage from rabbits differs somewhat from this. He was attempting to find out how long after death a homogenous transplant would be possible. A rabbit was killed and five pieces of auricular cartilage removed one hour after death. Two of these were placed on ice dry, and two moistened in Ringer's solution on ice. The fifth piece was implanted in the abdominal wall of another rabbit. Each hour up to six hours after death another piece of cartilage was removed and put in the abdomen of a living rabbit. At twenty-four hours and forty-eight hours the iced cartilage was implanted. Six months later the implants were removed and sectioned. They were all intact with the exception of the dry, iced cartilage. On section they all showed the cell spaces vacuolated and the nuclei absent. His conclusions were that the cartilage retained its form even though cellular death occurred.

It seems to me that the entire subject should be reviewed experimentally. A start has been made in this direction, the results of which are herewith reported.

#### METHOD OF EXPERIMENT 1

Since there seems to be ample clinical and experimental evidence that autogenous rib cartilage grafts live and maintain their size over prolonged periods of time, it might seem unnecessary to add further data. However, to establish a base line for the series of experiments planned it seemed essential that quantitative data should be obtained.

In dogs, central ossification of the costal cartilages occurs quite early. For this reason young adult dogs were used in order to secure rib cartilage with as little central bone as possible. If moderate calcification was found near the bony rib-cartilage junction, this end of the costal cartilage was trimmed off until only cartilage was left.

Ten dogs were used in this experiment, the operations being carried out aseptically under ether anesthesia. Each dog was operated upon in the same manner.

An oblique incision was made over the right and left costal margins, the rib cage exposed, and three costal cartilages removed on each side. The perichondrium was stripped off of three of these. The remaining

TABLE I  
AUTOGENOUS CARTILAGE TRANSPLANTS WITH PERICHONDRIUM

TIME GRAFT IN PLACE	ORIGINAL LENGTH AND WIDTH IN CM.	REMOVAL LENGTH AND WIDTH IN CM.	ORIGINAL WEIGHT IN GM.	REMOVAL WEIGHT IN GM.	CHANGE IN WEIGHT
2 wk.	6.7 × 0.6	8.0 × 0.4	0.808	0.508	-0.30
	6.2 × 0.7	6.1 × 0.6	1.143	0.857	-0.286
	5.6 × 0.3	5.7 × 0.2	0.192	0.180	-0.012
	7.4 × 0.5	7.6 × 0.4	0.918	0.960	+0.052
	6.8 × 0.6	6.5 × 0.5	0.810	0.783	-0.027
	5.2 × 0.45	5.0 × 0.4	0.282	0.216	-0.066
3 mo.	6.1 × 0.3	5.2 × 0.3	0.324	0.339	+0.005
	5.6 × 0.6	5.8 × 0.6	0.322	0.308	-0.014
	8.0 × 0.4	7.7 × 0.6	0.753	0.744	-0.009
	5.7 × 0.2	5.6 × 0.2	0.188	0.196	+0.008
	7.0 × 0.7	7.2 × 0.6	1.026	1.008	-0.008
	6.5 × 0.5	6.4 × 0.45	0.775	0.756	-0.019
6 mo.	5.0 × 0.5	4.8 × 0.5	0.181	0.207	+0.026
	6.0 × 0.3	5.8 × 0.3	0.315	0.336	+0.021
	6.2 × 0.6	6.2 × 0.5	0.988	0.978	-0.010
	5.5 × 0.6	5.7 × 0.6	0.308	0.329	+0.021
	6.7 × 0.6	6.9 × 0.5	0.810	0.867	+0.057
	7.0 × 0.4	7.0 × 0.5	0.623	0.638	+0.015
1 yr.	6.2 × 0.45	6.4 × 0.5	0.605	0.800	+0.195
	4.45 × 0.6	4.7 × 0.45	0.240	0.300	+0.060
	5.2 × 0.4	5.0 × 0.5	0.198	0.221	+0.023
	4.4 × 0.3	4.5 × 0.3	0.112	0.108	-0.004
	7.0 × 0.5	7.0 × 0.5	0.776	0.728	-0.048
	6.5 × 0.4	6.4 × 0.4	0.561	0.532	-0.029
1½ yr.	5.6 × 0.6	4.5 × 0.5	0.311	0.222	-0.089
	5.5 × 0.5	5.6 × 0.5	0.704	0.669	-0.035
	7.6 × 0.7	7.0 × 0.7	0.610	0.531	-0.079
	5.5 × 0.5	5.0 × 0.5	0.305	0.261	-0.044
	6.0 × 0.5	5.8 × 0.4	0.588	0.517	-0.071
	5.0 × 0.5	4.7 × 0.5	0.196	0.181	-0.015

three were cleared of soft tissues as completely as possible, but the perichondrium was not disturbed. A small piece of each rib cartilage was saved for microscopic examination. Each segment of cartilage was measured, the length and breadth at the widest point recorded, and the weight determined on a chemical balance. The three cartilages with perichondrium were implanted in the subcutaneous tissues of the abdomen on the right side. One was placed in the epigastrium, one opposite the umbilicus, and one in the lower abdomen. The three without perichondrium were placed in parallel positions in the left anterior abdominal wall. Each piece of cartilage was inserted through a separate small incision one-half to one inch long. These wounds and the ones over the costal margins were closed with silk.

In all, sixty transplants were made, thirty with and thirty without perichondrium. The grafts were removed from two dogs at intervals of two weeks, three months, six months, one year, and one and one-half years. Thus six grafts with perichondrium and six grafts without perichondrium were made available for study at each time interval.

TABLE II

## AUTOGENOUS CARTILAGE TRANSPLANTS WITHOUT PERICHONDRUM

TIME GRAFT IN PLACE	ORIGINAL LENGTH AND WIDTH IN CM.	REMOVAL LENGTH AND WIDTH IN CM.	ORIGINAL WEIGHT IN GM.	REMOVAL WEIGHT IN GM.	CHANGE IN WEIGHT
2 wk.	7.7 × 0.5	8.1 × 0.5	0.909	0.740	-0.169
	6.5 × 0.6	5.9 × 0.35	0.329	0.188	-0.141
	6.0 × 0.5	6.0 × 0.5	0.308	0.295	-0.013
	5.5 × 0.4	5.7 × 0.4	0.288	0.178	-0.110
	4.2 × 0.3	4.5 × 0.3	0.115	0.128	+0.013
	7.8 × 0.5	8.2 × 0.5	0.875	0.712	-0.163
3 mo.	4.0 × 0.3	3.4 × 0.3	0.102	0.072	-0.030
	6.1 × 0.5	5.8 × 0.5	0.311	0.260	-0.051
	8.1 × 0.5	7.8 × 0.4	0.928	0.857	-0.071
	5.1 × 0.3	5.3 × 0.3	0.258	0.277	+0.019
	6.5 × 0.4	6.5 × 0.4	0.308	0.288	-0.020
	8.0 × 0.5	7.5 × 0.5	0.905	0.866	-0.039
6 mo.	5.0 × 0.25	5.0 × 0.3	0.204	0.217	+0.013
	7.5 × 0.5	7.8 × 0.5	0.878	0.905	+0.027
	4.8 × 0.3	5.0 × 0.3	0.197	0.205	+0.008
	7.0 × 0.6	7.4 × 0.6	0.585	0.631	+0.046
	4.6 × 0.4	5.2 × 0.5	0.312	0.388	+0.076
	8.0 × 0.5	7.5 × 0.4	1.021	0.975	-0.046
1 yr.	6.5 × 0.55	7.4 × 0.4	0.352	0.361	+0.009
	6.2 × 0.35	7.0 × 0.5	0.347	0.352	+0.005
	5.4 × 0.45	5.0 × 0.35	0.408	0.356	-0.052
	6.0 × 0.5	6.5 × 0.4	0.360	0.355	-0.005
	7.8 × 0.35	7.5 × 0.35	0.516	0.505	-0.011
	4.5 × 0.3	4.0 × 0.3	0.155	0.098	-0.057
1½ yr.	6.5 × 0.6	6.0 × 0.6	0.225	0.300	+0.075
	7.8 × 0.5	8.2 × 0.6	0.617	0.552	-0.065
	7.5 × 0.5	8.0 × 0.5	0.605	0.568	-0.037
	5.0 × 0.3	4.8 × 0.3	0.215	0.230	+0.015
	6.2 × 0.5	6.4 × 0.55	0.355	0.346	-0.009
	7.5 × 0.5	7.8 × 0.45	0.587	0.550	-0.037

## GROSS EXAMINATION AND MEASUREMENT OF TRANSPLANTS

During the course of the experiment the transplants could be easily palpated under the skin and in most instances their outlines were visible. No graft was absorbed; all were recovered and studied. On removal it was found that they were rather loosely attached in the subcutaneous tissues. If on removal any soft tissue remained adherent, this was removed as carefully as possible. Inspection showed that the transplants still retained their cartilaginous characteristics. The grafts which had been longer in their new location in some instances showed small areas which had lost their translucent sheen. These spots were yellower than the surrounding hyaline-appearing cartilage and softer. In all instances the transplants were pliable and when bent still retained their springlike elasticity. The specimens were measured and it was found that their dimensions were practically the same as when originally transplanted. There were minor variations, but these were within the limits of error. The specimens were also weighed for comparison with the weights recorded at time of transplantation. It was found, here too,

that little change had occurred. In general both those grafts with and without perichondrium showed their greatest weight loss in the specimens removed two weeks after grafting. A minor weight loss was also noted in the three-month specimens. On the other hand, those grafts removed six months after transplantation showed on the whole a small gain in weight. There was then a small weight loss in general in those specimens which had been transplanted for a year and for one and one-half years. There was no significant difference in the quantitative be-



Fig. 1—Photomicrograph ( $\times 100$ ), showing the architecture normally seen in costal cartilage of young adult dogs.  
A, With perichondrium, B, without.

havior or the gross appearance in those grafts transplanted with, and those transplanted without, perichondrium.

The detailed data appear in Tables I and II.

#### MICROSCOPIC EXAMINATION

Sections were made for microscopic examination of all sixty grafts. The photomicrographs shown are representative ones selected from those studied at the various time intervals.

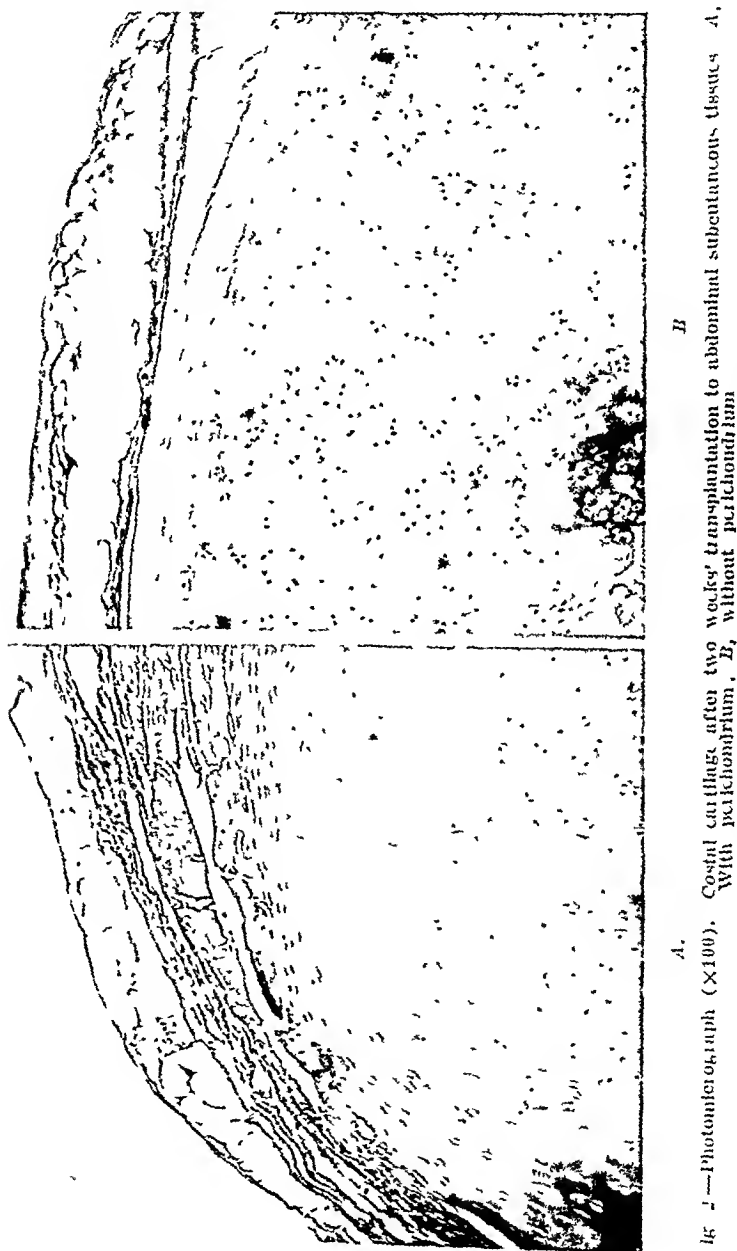


Fig. 2.—Photomicrograph ( $\times 100$ ). Costal cartilage after two weeks' transplantation to abdominal subcutaneous tissues. A, With perichondrium; B, without perichondrium.

One can state without question that these autogenous cartilage grafts remain living cartilage. In all specimens the cellular structure was found intact and cell nuclei present. As the grafts were in their new location for longer periods the cells in most instances appeared larger with a greater amount of clear area about the nuclei. In the older specimens central calcification was frequently observed, and in some in-

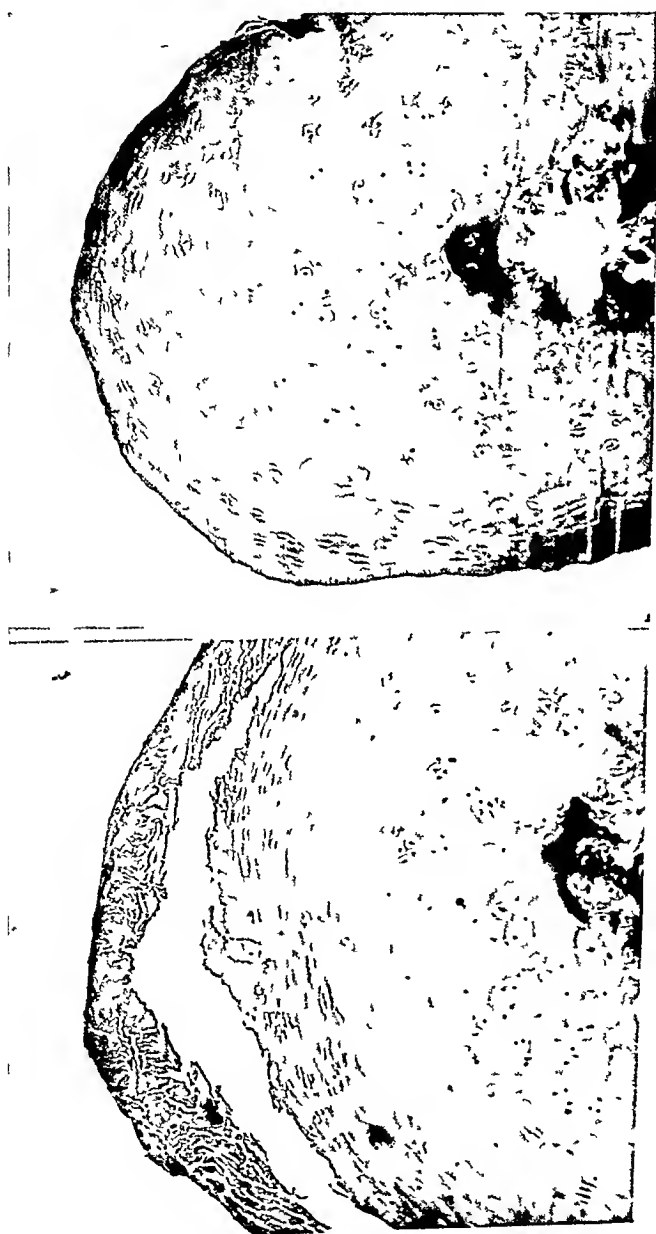


FIG. 3.—Photomicrograph (X100). Specimens of costal cartilage removed after three months in abdominal wall. A, With perichondrium shows moderate central calcification. B, transplanted without perichondrium also shows this. In both specimens there is some increase in the clear zones about the cell nuclei.

stances osteoid or actual bone formation occurred. In this centrally formed bone a marrow cavity was at times observed.

## EXPERIMENT 2

While engaged in the foregoing experiment which is intended as a baseline experiment for similar studies to be carried out with living

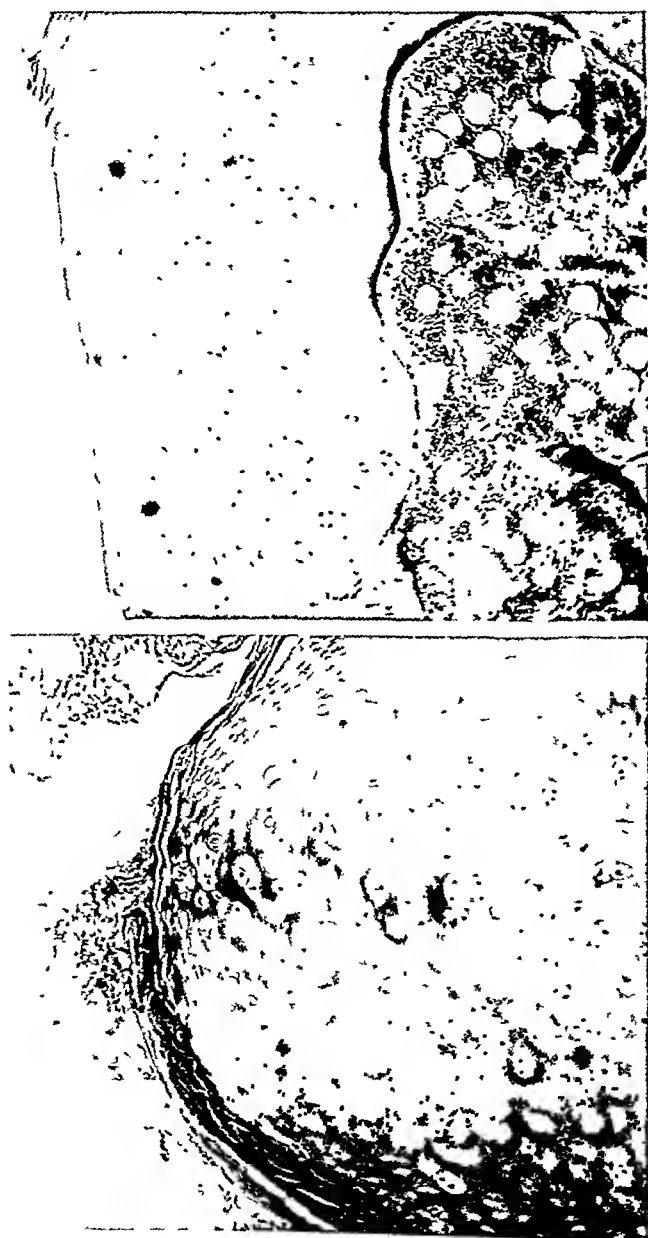


Fig. 1—Photomicrograph (X100). Specimens removed from abdominal wall at six months. A, Transplanted with perichondrium, shows moderate increased size of the clear zones of the cells, B, transplanted without perichondrium, central bone marrow formation.

homogenous and zoögenous grafts and with dead autogenous, homogenous, and zoögenous implants, it occurred to me that it might be possible to grow thin sheets of cartilage by seeding small particles of living autogenous cartilage in a known location. Although this at first thought might seem to have little prospect of success, I had some encouragement from experiments previously completed<sup>9</sup> in which it had been observed

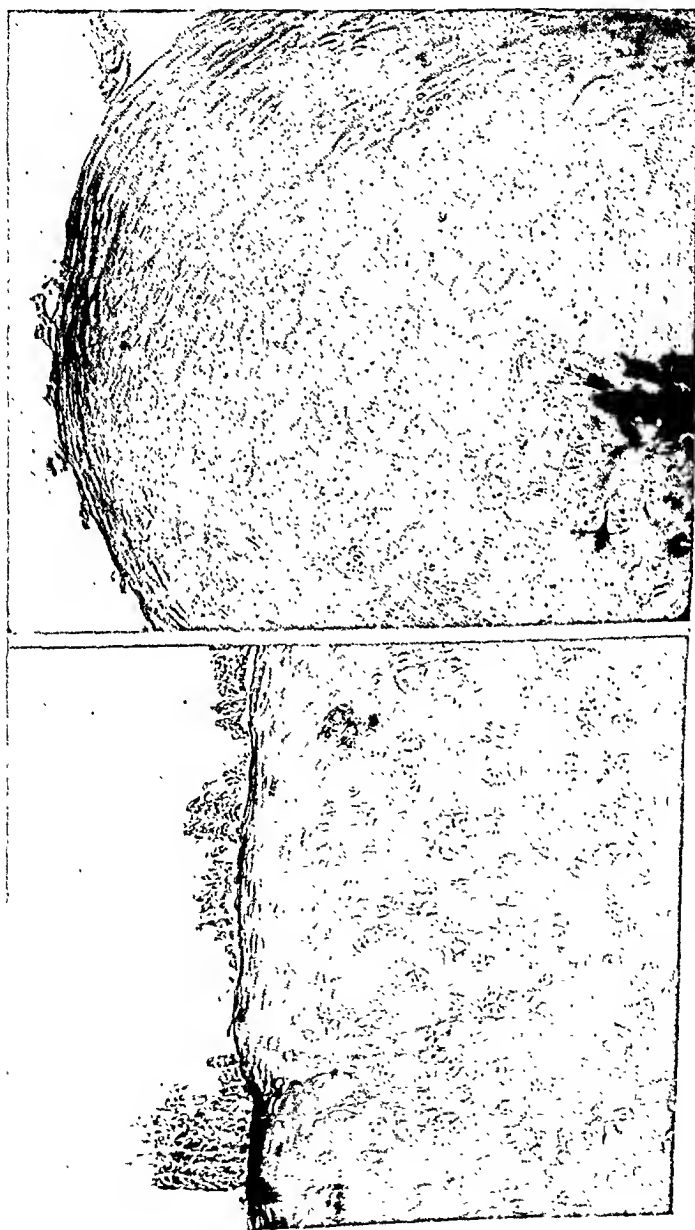


FIG. 5.—Photomicrograph ( $\times 100$ ). Specimens removed from abdominal wall at one year. Both A (without perichondrium) and B (with perichondrium) are well preserved.



that strips of rib cartilage placed side by side in the dog's knee joint seemed to heal together by cartilaginous fusion.

#### METHOD

Accordingly costal cartilages were removed as in the previous experiment. From one-half of these the perichondrium was removed. The cartilage was then chopped into fine particles. On the right side of the

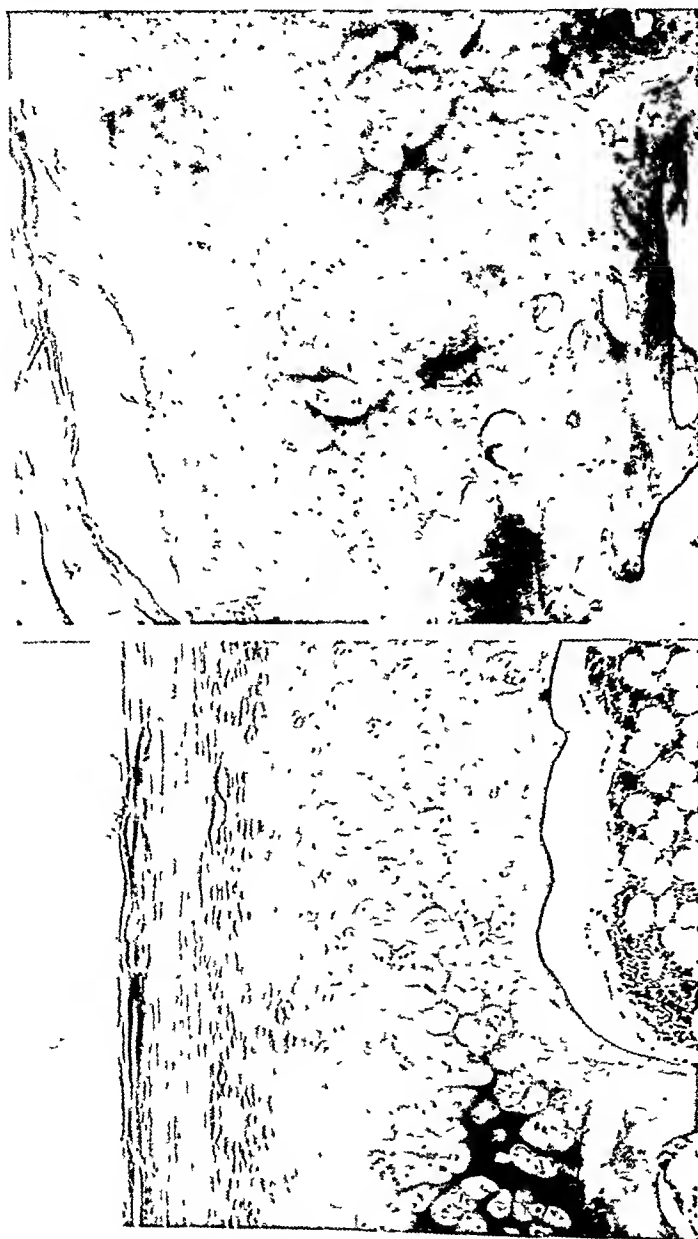


Fig. 6—Photomicrograph ( $\times 100$ ). Specimens removed from abdominal wall one and one-half years after transplantation. Both A (with perichondrium) and B (without perichondrium) show moderate degenerative changes. There is central bone and marrow formation and some peripheral fibrous tissue invasion.

abdomen small incisions were made down to the rectus fascia, and the subcutaneous tissues separated from the fascia to make a small pocket. On the right side the chopped cartilage with perichondrium was placed in three depots, one on the upper, mid-, and lower abdomen. Chopped cartilage without perichondrium was placed in similar locations on the left side. This finely divided cartilage was spread out in a thin layer over the rectus fascia so that an area about one inch in diameter was covered and the subcutaneous tissues lay smoothly over it. The wounds were closed with silk. Four dogs in all were operated upon. The wounds were then opened at intervals of three months, six months, one year and one and one-half years.

#### GROSS APPEARANCE

Twenty-four specimens in all were examined, twelve with and twelve without perichondrium. In each instance a thin sheet of glistening, translucent, cartilaginous-appearing material about the size and shape of a half-dollar was recovered. Tiny rounded protuberances could be seen

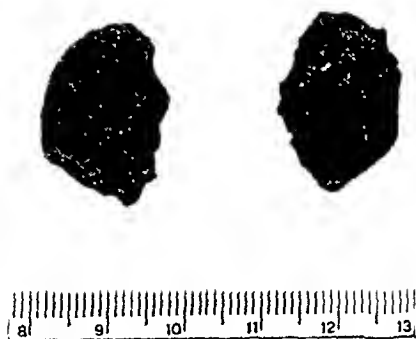


Fig. 7.—Gross appearance of masses removed at one and one-half years, following seeding of cartilage particles in a pocket over the rectus fascia.

on the homogenous surface of this mass which probably represented individual particles of cartilage. This thin sheet of opaque cartilaginous-appearing material had the springlike quality of cartilage. It could be bent to 50 to 60° without cracking and on release return to its original position and shape.

#### MICROSCOPIC EXAMINATION

These specimens were all sectioned and studied. It was found that there was no actual growth of cartilage of which one could be positive, but the particles of cartilage had become adherent to one another by fibrous tissue. The cartilage particles were all living as evidenced by the character of the cells. In the one-year and one-and-one-half-year specimens there was considerable bone and marrow formation noted in some of the cartilage particles.

## CONCLUSIONS

From the two experiments reported it would appear that autogenous rib cartilage when transplanted to the subcutaneous tissues of the dog remains living and maintains its size and weight for as long as one and one-half years.



Fig 8—Photomicrograph (X8) Cross-section of specimen removed six months after seeding cartilage particles. The cartilage particles are connected by loose fibrous tissue.



Fig 9—Photomicrographs (X8) Specimen of cartilaginous mass produced by seeding which was removed at one and one-half years. There is bone formation in the center of most of the cartilage particles.

Autogenous rib cartilage, finely chopped and seeded over the rectus fascia in the dog, stays viable and fuses together into a solid sheet of opaque cartilage-like material. This fusion is by fibrous tissue. Grossly this mass has some of the properties of fibroelastic cartilage.

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# STUDIES OF THE JUGULAR PRESSURE OF ANESTHETIZED DOGS DURING POSITIVE INFLATION OF THE LUNGS BEFORE AND AFTER PNEUMONECTOMY

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the Presbyterian Hospital)*

AS THE use of positive pressure anesthesia is being extended, the dangers that accompany its administration should be more generally appreciated. Recent discussions of the subject direct attention to the impairment of ventilation when positive pressure is continuous<sup>1</sup> and emphasize the importance of avoiding high pressures because of the danger of rupturing alveoli.<sup>2,3</sup> The effects of positive pressure ventilation on the circulation, however, seem to have been overlooked, or passed over in a few words. After emphasizing the mechanical effectiveness of his positive pressure apparatus, Crafoord,<sup>1</sup> for example, warns that "the only thing we have to follow closely is the circulation." He then dismisses the subject with just one additional sentence, in which he states that any failure of the circulation can be easily corrected by the intravenous administration of blood and stimulants.

In some of our previous studies it was shown that inflation of the lungs of anesthetized dogs caused a fall in cardiac output. In the first series of experiments this decrease in cardiac output was observed after thoracotomy and inflation of the lungs at pressures varying between 3 and 6 mm. of mercury.<sup>4</sup> In later experiments it was demonstrated that the decrease in cardiac output was proportional to the intratracheal pressure used.<sup>5</sup> Further studies have shown that a rise in both jugular vein and pulmonary artery pressures also occurs and that a similar rise in pulmonary artery pressure follows ligation of the pedicle of one lung.<sup>6</sup> Because in experiments done previous to all of these<sup>7</sup> it had been demonstrated by us that ligation of either primary branch of the pulmonary artery did not cause a change in cardiac output, it was suggested that the reduction in cardiac output accompanying positive pressure inflation was due to a tamponade effect caused by pressure of the inflated lungs on the mediastinum and heart rather than to pulmonary artery obstruction. Confirmation of this hypothesis is

<sup>7</sup>Presented at the meeting of the Society of University Surgeons, at St. Louis, Mo., Feb. 14 and 15, 1911.

here presented by studies of the effect on venous pressure of inflation of the left lung after eliminating the possibility of tamponade by resecting the right.

### METHOD

Direct measurements of the jugular pressure of five dogs, anesthetized with barbitol sodium, were obtained with the apparatus of Moritz and von Tabora.<sup>8</sup> Because the base line cannot be very accurately adjusted to the level of the base of the heart, the absolute values of these measurements are of less interest than their relative changes, which are not affected by the base line, under the experimental conditions.

In every experiment a control reading was obtained with the anesthetized animal breathing normally. The trachea was then connected tightly with a metal cannula, through the inspiratory arm of which oxygen was introduced by means of a catheter passed loosely into the trachea as far as its bifurcation. A second control reading was obtained immediately after cannulation of the trachea with the animal breathing oxygen at atmospheric pressure. Arrangements were then made for controlling intratracheal pressure by means of a screw clamp on the expiratory arm of the cannula. Intratracheal pressure was measured by direct connection of the cannula with a water manometer. After the second control reading had been obtained, the intratracheal pressure was raised to about 3 cm. of water and the chest was opened wide by splitting the sternum and introducing a self-retaining retractor.

Then, with the chest wide open, a series of venous pressure readings was obtained while both lungs were inflated by increasing pressures. Each pressure was maintained for only two minutes. The right lung was then resected by clamping, dividing, and ligating the hilar structures of each lobe separately. A second series of venous pressure readings was then obtained while the left lung was inflated by increasing pressures. Since this procedure resulted in varying degrees of mediastinal distortion, with marked displacement of the heart to the right side, in the last three experiments a third series of venous pressure readings was obtained after opening the pericardium and holding the heart in its normal position with a silk suture passed through its apex.

### RESULTS

Inflation of the lungs in the open chest preparation was regularly followed by an immediate increase in venous pressure. Within limits this increase in venous pressure was directly proportional to the degree of intratracheal pressure used. Furthermore, the curve of venous pressure response was a highly individual one for each animal studied so that the readings must be plotted separately. All of these changes have been observed by us in previous experiments,<sup>7</sup> and they constitute the control observations for the experiments reported in this paper.

When the venous pressure readings were repeated after resection of the right lung, the results were strikingly different. Under these conditions and with the same intratracheal pressures, venous pressure rose very little and when displacement of the heart was prevented the venous pressure change was even less. The failure of venous pressure to rise after resection of the right lung, however, was observed only within certain limits of intratracheal pressure. If intratracheal pressure was carried above these limits the right heart failed and then, as one would expect, the venous pressure rose rapidly until the circulation came to a standstill.

The results are shown graphically in Figs. 1 and 2.

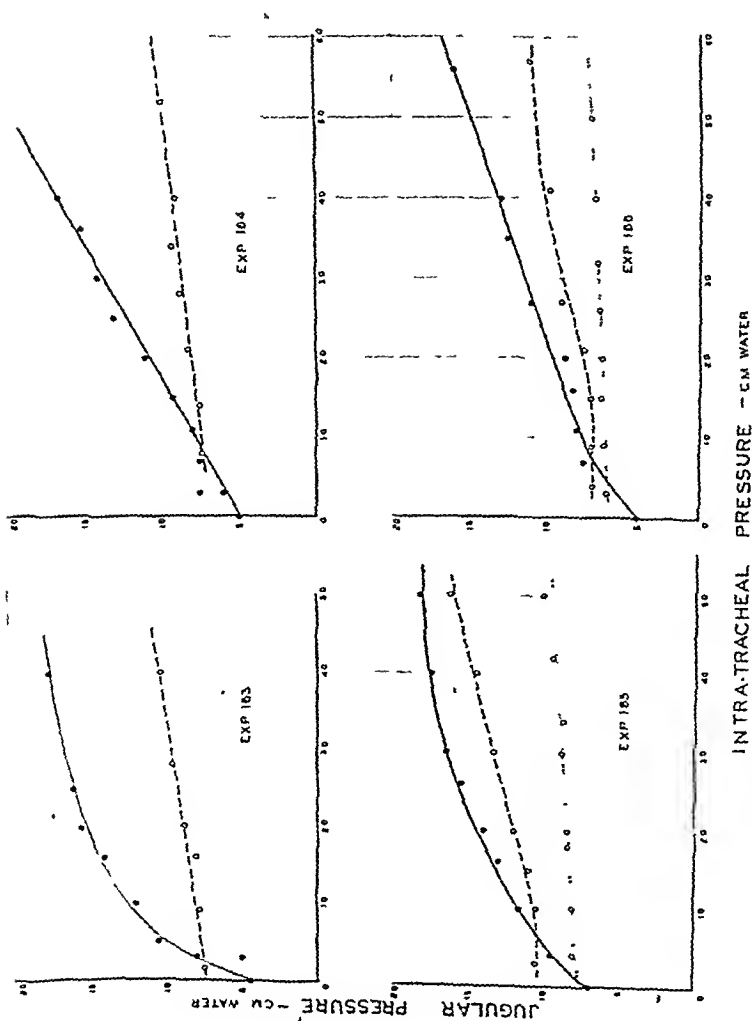


Fig. 1.—Venous pressure readings in the first four experiments plotted graphically against the intratracheal pressure. The solid line represents the changes in venous pressure when both lungs were present; broken line, the changes after resection of the right lung, and dotted line, the changes after resection of the right lung and immobilization of the heart. When both lungs were present, the rise in venous pressure was immediate and marked; after resection of the right lung, the rise was gradual and slight; and, finally, after resection of the right lung and immobilization of the heart, the rise was negligible.

## DISCUSSION

Experimental studies have repeatedly shown that during gradual occlusion of the pulmonary artery there is no damming back of blood in the peripheral veins until heart failure occurs.<sup>9, 10</sup> Recently Mendlowitz<sup>11</sup> has demonstrated again that a normal dog's heart is capable of overcoming a very high degree of pulmonary arterial block without appreciable change in peripheral venous pressure. Our experiments were similar since inflation of the lungs at high pressures introduced a resistance to the pulmonary blood flow which was equivalent to blocking partially the main trunk of the pulmonary artery. When tamponade was prevented by resecting the right lung, there was no significant rise in

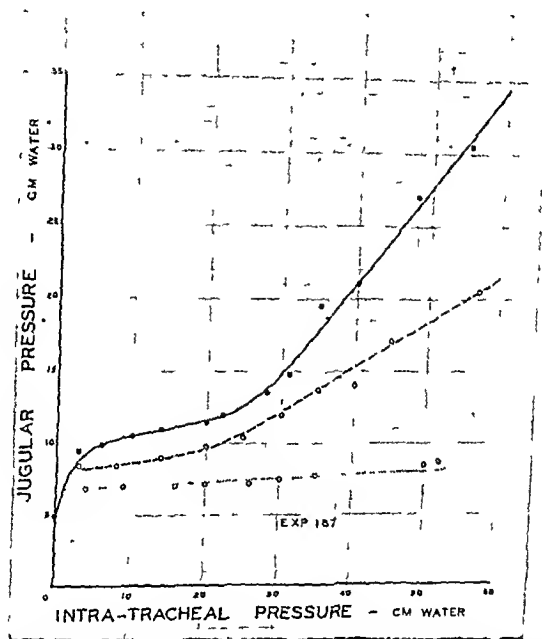


Fig. 2.—Venous pressure readings in the fifth experiment. In this animal venous pressure rose to an unusual height when both lungs were present (solid line), considerably less after the right lung had been removed (broken line), and almost none after the pericardium had been opened and heart held in normal position (dotted line).

venous pressure until the right heart failed. When both lungs were present, however, the venous pressure rose in direct proportion to the intratracheal pressure used. It is apparent, therefore, that the rise in venous pressure which accompanies inflation of the lungs cannot be attributed to the inability of the heart to overcome the increase in resistance in the pulmonary circulation which occurs at the same time.

Mediastinal emphysema was not observed in any of these experiments, although pressures well above those reported to cause it<sup>3</sup> were used, possibly because each pressure was maintained for only two minutes. If an early and overlooked alveolar rupture and emphysema did take



place, it cannot have been responsible for the rise in venous pressure, since the latter fell again as soon as the intratracheal pressure was lowered. Since the oxygen and carbon dioxide contents of the arterial blood were not studied, it is not known whether resection of the lung was followed by anoxia or accumulation of carbon dioxide due to impaired ventilation. Nevertheless, since the rise in venous pressure which accompanied inflation of both lungs did not occur after one had been resected, it cannot be attributed to anoxia or accumulation of carbon dioxide. It must be concluded, then, that a tamponade effect, caused by compression of the heart or great vessels between the expanding lungs, was responsible for the venous pressure rise when both lungs were present. When one lung was resected, there was no tamponade effect and consequently no rise in venous pressure.

The consistent finding of a high degree of individual variation in the type of venous pressure response, although its direction was always the same, is of interest. It seems probable that the shape of each animal's chest as well as age and general condition are determining factors.

Since the shape of the chest of a human being is very different from that of a dog, the tamponade effect produced by positive pressure anesthesia must differ in degree from that demonstrated in these experiments. It must, however, be similar and presumably shows similar individual variations. For this reason it cannot be said that one intratracheal pressure is safe and another dangerous. What is safe for one patient may be dangerous for another, and must vary for the same patient under different circumstances.

#### SUMMARY AND CONCLUSIONS

The jugular vein pressure of five anesthetized dogs was measured after opening the chest wide and inflating the lungs continuously at increasing pressures. The right lung was then resected by ligating and dividing the pedicle of each lobe separately, and the response of the venous pressure to similar intratracheal pressures was again observed. Finally, in three animals, a third set of venous pressure readings was obtained after the pericardium had been opened wide and the heart fixed in normal position by a suture through its apex.

The findings were as follows:

1. When both lungs were inflated at increasing intratracheal pressures, the jugular vein pressure rose in every experiment.
2. The rise in venous pressure was less abrupt and much less marked after resection of the right lung.
3. When, following resection of the right lung, the pericardium was opened and heart fixed in normal position, the rise in venous pressure did not occur until the right heart failed.

We believe these findings show conclusively that the decrease in cardiac output, which has been shown to accompany positive inflation

of the lungs in experimental animals, is due to compression of the heart and interference with its filling rather than to compression of the pulmonary vessels and interference with its emptying.

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## OBSERVATIONS ON THE USE OF PROLONGED ANESTHETIC AGENTS IN UPPER ABDOMINAL INCISIONS

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IT HAS long been suspected that the limitation of respiratory excursions due to pain is an important factor in the relatively high incidence of pulmonary complications following operations on the upper abdomen. In his experiments Kahn has shown that stimulation of the central end of any intercostal nerve causes a reflex inhibition of respiration. Particularly is this true of the seventh to twelfth intercostal nerve. Similarly, stimulation of the peripheral branches, including those to rectus abdominus muscle, inhibits respiration. Cutler and Hoerr have shown that this inhibition is greater than is perhaps generally realized, amounting to a 59 per cent depression of the mean vital capacity during the first few postoperative days.

The ordinary prophylactic measures, such as the avoidance of tight dressings, rebreathing with carbon dioxide, and frequent changes of position, employed to prevent or decrease the incidence of pulmonary complications, are effective only up to a certain point. To a considerable extent they are necessary only because the patient is either unable or unwilling to take a deep breath, to cough, or to move about in bed because of the pain arising from the surgical incision. It seems reasonable, therefore, that if the pain in the wound were alleviated sufficiently during the first few postoperative days, the patient would be more comfortable and the surgeon would have fewer pulmonary complications to contend with.

Many methods have been advocated to minimize the pain of surgical incisions. One approach has been directed at placing the incision in such a fashion as to interfere with as few sensory nerves as possible. Transverse incisions have accordingly been recommended by many surgeons.

As another approach to the problem, various types of anesthetic agents have been administered by a variety of methods and in a variety of locations. The use of anesthetic agents to alleviate the pain of surgical incisions over a prolonged period is by no means a new idea. Many years ago Crile,<sup>1, 2</sup> recommended the injection about the wound of quinine and urea hydrochloride in a  $\frac{1}{16}$  to  $\frac{1}{2}$  per cent solution. Although a satisfactory anesthesia lasting for several days resulted, the method was discarded because it produced fibrinous exudate with occasional suppuration at the sites of injection.

<sup>1</sup>Presented at the meeting of the Society of University Surgeons at St. Louis, Feb. 11 and 12, 1911.

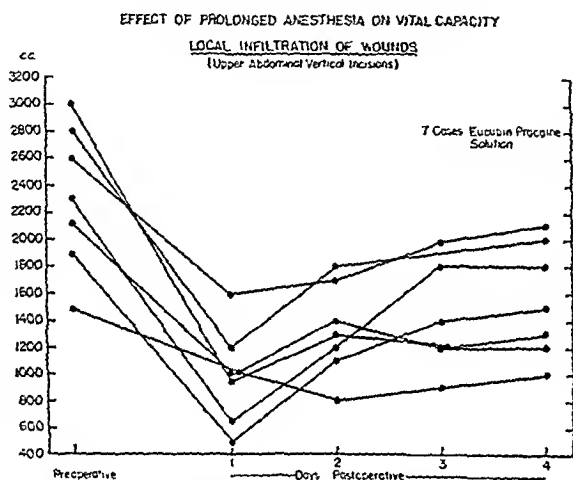
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was our clinical impression that these patients were more comfortable after operation and required less sedation than the average. But it is admittedly difficult to evaluate the amount of discomfort that patients experience after operation, for this varies according to the age, sex, and mental make-up of the individual. And of the amount of sedation given, such as morphine, is unreliable, these sedatives may be prescribed for restlessness or to insure sleep, not for pain in the wound.

One of the simplest and most reliable methods of determining the amount of pain following upper abdominal incisions is a record of the vital capacity. Cutler and Hoerr have shown that there is invariably a marked reduction in vital capacity after a high abdominal incision. Their figures were used by us as a control on the effectiveness of the method in increasing the respiratory excursions.



1.—Graph of vital capacities before and after operation when eucupin-procaine solution was infiltrated locally.

In Fig. 1 is tabulated the vital capacity of patients whose upper abdominal wounds were infiltrated with eucupin-procaine solution. The vital capacity was recorded before and on succeeding days after operation. There was no significant variation as compared to the control cases. Influenced by Bartlett's excellent report on the efficiency of intercostal nerve block for upper abdominal surgery, we studied the possibility of obtaining prolonged anesthesia by substituting an anesthetic in place of novocain in intercostal nerve block. Burt and Gius, through experiments in animals, had shown that certain anesthetic agents in oil (ethesol) did not retard wound healing or increase the incidence of infection. Bartlett showed how the anatomical arrangement of the intercostal space, especially about the midaxillary line, lends itself to the application of nerve block anesthesia. The intercostal nerve in this location is in a closed compartment just beneath the inferior margin

Capelle, a few years ago, recommended the continuous administration of novocain to overcome the pain in surgical wounds and to increase the postoperative vital capacity. He employed an ingenious apparatus, consisting of several large, thin, curved, hollow needles attached to a tube. These needles he inserted after closure of the peritoneum, in a fashion similar to the placement of retention sutures, thereby providing a tubular irrigation system for injecting the anesthetic agent as required. He found that the irritation from the needles was no more marked than that produced by wire retention sutures. Although this method may be effective in producing anesthesia in the wound over a prolonged period of time, it presents many obvious undesirable features.

Gius, impressed with Capelle's results, which showed a return of vital capacity from the usual 20 to 40 per cent of normal immediately after operation to 90 per cent of normal when the wound was anesthetized, adopted a paravertebral procaine block in the treatment of postoperative atelectasis. He reported the use of this paravertebral block of the lower thoracic and upper lumbar nerves in two children, who developed atelectasis following appendectomy. Both were relieved of their pain in the abdominal wound, and as a result could cough vigorously without distress. It was his impression that temporary abolishment of pain in the wound allowed hyperventilation of the lungs and effective coughing.

Although in our preliminary studies at the time of closure we injected an anesthetic in oil in the layers of the abdominal wall adjacent to the incision, we hesitated to use an amount sufficient to insure complete anesthesia of the wound. So we sought an agent which could be prepared in aqueous solution, and which would give prolonged anesthesia. On the basis of some observations by de Takats and Collins on the effectiveness of eucupin as a prolonged anesthetic, this material was selected. The solution used consisted of eucupin dihydrochloride 0.06 Gm., procaine hydrochloride 0.30 Gm. in Ringer's solution to make 30 c.c.\* The procaine was added to give immediate anesthesia and to overcome the burning sensation that accompanies the injection of eucupin.

The effectiveness of local infiltration of eucupin-procaine solution was studied in a group of patients who had been submitted to gastric or biliary operations through vertical upper abdominal incisions. At the time of closure of the abdominal wound, while the patient was still under general anesthesia, the eucupin-procaine solution was injected locally about each side of the incision. No intradermal infiltration of the skin was carried out, but when retention sutures were used, infiltration was carried out about these as well. Although the amount injected was variable, it usually amounted to 50 c.c.

\*The chemical used in these experiments was supplied by the Kure Chemical Co., Nepara Park, N. Y.

It was our clinical impression that these patients were more comfortable after operation and required less sedation than the average patient. But it is admittedly difficult to evaluate the amount of discomfort that patients experience after operation, for this varies according to the age, sex, and mental make-up of the individual. A record of the amount of sedation given, such as morphine, is unreliable, because sedatives may be prescribed for restlessness or to insure sleep, and not for pain in the wound.

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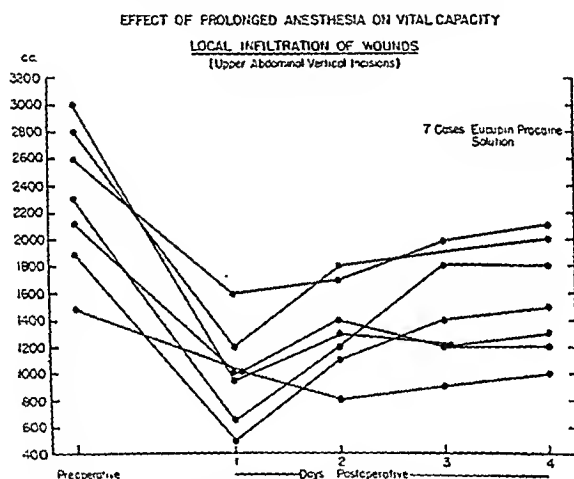


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of the rib between the external and internal intercostal muscles. This anatomical arrangement permits the use of relatively small amounts of an anesthetic solution with reasonable assurance of an effective nerve block. The anesthetic selected was eucupin base, 0.005 Gm.; ethyl aminobenzoate, 0.15 Gm.; benzyl alcohol, 0.25 Gm.; and sufficient oil of sweet almond to make 5 c.c.

The method of producing the intercostal block we employed was essentially that described by Bartlett. The side to be injected was elevated by a sandbag or pillow under the chest, and the arm was abducted (Fig. 2). It is helpful, especially in females with pendulous breasts or in obese individuals, in locating the inferior margin of the rib where the injection is to be given, to have the skin of the abdominal wall held

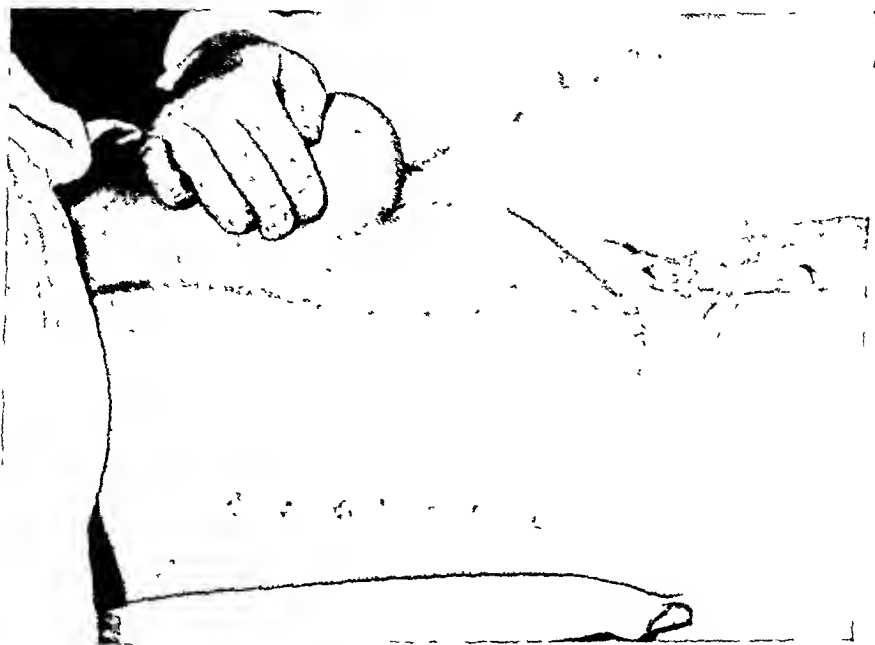


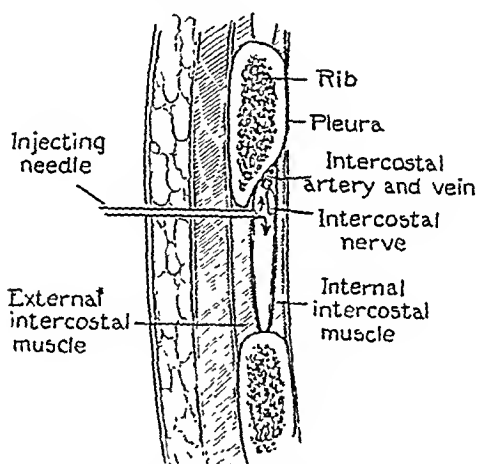
Fig. 2.—Location of points of injection for intercostal anesthesia.

taut by an assistant. The lateral chest wall was well elevated to permit injection in the midaxillary line or slightly posterior, because in the usual position on the operating table we have found that there is a tendency for the injection to be made too far forward on the chest wall to assure a satisfactory block anesthesia. After the skin is suitably prepared and the anesthetic in oil has been warmed, the injection is made with a No. 19 needle. One can feel the needle pass beneath the inferior margin of the rib and through the fascia covering the external intercostal muscle (Fig. 3). The point of the needle should then be in the compartment between the two intercostal muscles adjacent to the intercostal nerve, but to make sure that the point of the needle has not



entered the pleural cavity repeated attempts are made to withdraw the plunger. The injections were usually started at the eleventh rib and continued upward to include all the intercostal nerves as far as the fifth or sixth, depending upon how high the upper abdominal incision was to be carried.

Varying amounts of eneupin solution in oil, from 1.5 to 5 c.c., were injected into the individual intercostal spaces. Effective nerve block probably does not depend so much upon the amount of anesthetic in oil which is used as upon accurate injection of the solution in relation to the intercostal nerves. For example, the best result we obtained came after an injection of only 1.5 c.c. into each intercostal space. For right rectus incisions in procedures on the biliary system, we have used the block anesthesia on one side only. However, if the incision was made near the midline and retention sutures were used, bilateral nerve block was carried out, as it also was for midline incisions or those slightly to the left of the midline.



Diagrammatic Section  
Through Midaxillary Line

Fig. 3.—Illustration of point of injection, the closed intercostal space (after Bartlett).

Since the introduction of the intercostal block is not without some discomfort to the patient, we now prefer to introduce it after the patient is asleep or at the end of the operation. However, until the technique was acquired, we carried out blocking before the induction of general anesthesia. This insured complete anesthesia of the field, for the effectiveness of the anesthesia over the upper abdomen could be checked by needle prick, and if the anesthesia was not complete, the injection could be repeated as necessary. In addition, this permitted us to test the completeness and effectiveness of the nerve block by opening the abdomen without additional anesthesia. In these instances we noted a tendency toward increased bleeding in the wound. Except for the

of the rib between the external and internal intercostal muscles. This anatomical arrangement permits the use of relatively small amounts of an anesthetic solution with reasonable assurance of an effective nerve block. The anesthetic selected was eucupin base, 0.005 Gm.; ethyl aminobenzoate, 0.15 Gm.; benzyl alcohol, 0.25 Gm.; and sufficient oil of sweet almond to make 5 c.c.

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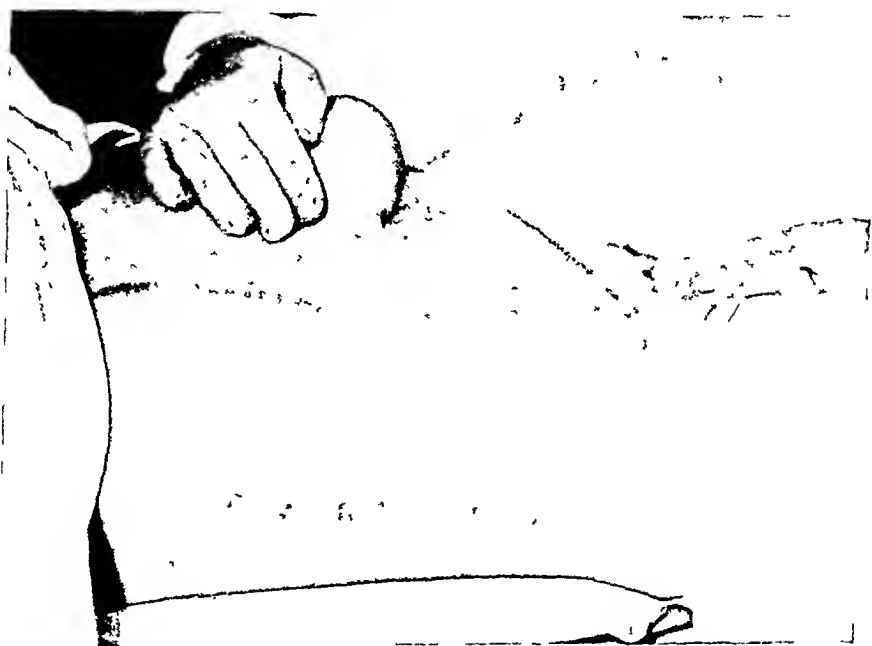


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to the eleventh intercostal space in the midaxillary line on the right side. Only in 1 patient was a bilateral block produced.

Fig. 4 presents the vital capacities of these patients before operation and on the four days immediately following operation contrasted to those of 48 women on whom similar operations were carried out without intercostal block anesthesia. The majority of the patients had a vital capacity greater than the median vital capacity attained by any 1 of the 48 in the control group. The vital capacity of 1 female quite remarkably was not below 3,000 c.c. after operation. Six of the 10 were above the maximum on the first postoperative day, while 1 equalled the maximum and 3 were below.

#### EFFECT OF PROLONGED INTERCOSTAL ANESTHESIA ON VITAL CAPACITY

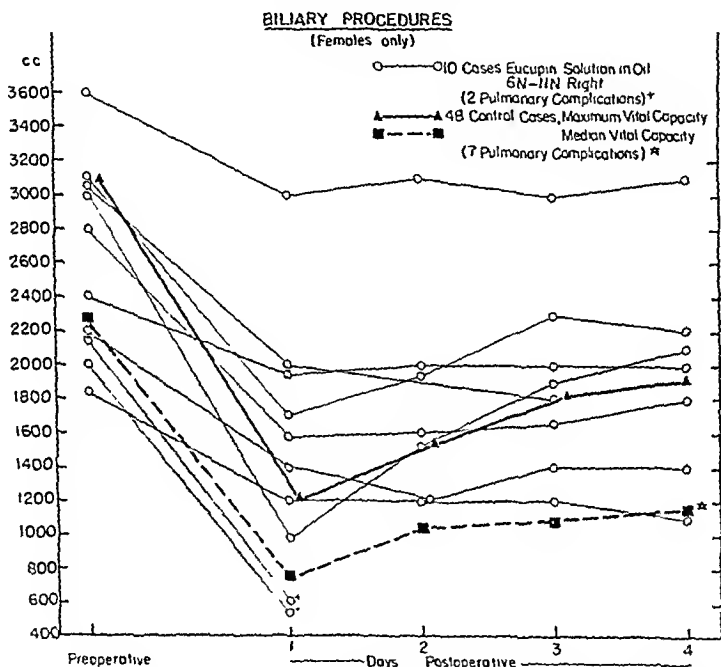


Fig. 4.—Comparison of vital capacities of 48 control cases before and after biliary operations with 10 cases in which eucupin solution in oil was injected intercostally on the right side.

Two patients, 1 with a bilateral block, complained of pain immediately after recovery from the general anesthesia, required morphine in repeated doses, and showed signs of pulmonary atelectasis within twenty-four hours of operation. Further vital capacity readings were not taken on these 2 patients. As far as we could determine, the block had failed and had no effect upon the pain from the surgical incision.

An x-ray of the chest, taken eight days after operation in the patient with bilateral block, showed fairly marked clouding, together with some fluid at the right base but no displacement of the heart or trachea. The left side was clear. A diagnosis of bronchopneumonia and pleural

peritoneum, the abdominal wall was, as a rule, anesthetized satisfactorily. The operation was then continued under general anesthesia. The induction of the block anesthesia in the conscious patient also permitted studies of vital capacity to determine whether interference with the motor innervation in the involved intercostal or upper abdominal muscles lowered the vital capacity. No significant change in the vital capacity was found.

One question which naturally arises is whether or not the introduction of an anesthetic in oil containing benzyl alcohol produces an undesirable reaction in the adjacent pleura or the pleural cavity, should it be accidentally injected therein. Although we have not been able to detect any noteworthy reactions in patients, some local reaction must occur judging from observations in animals.

Eucupin solution in oil was injected intercostally in dogs, following a technique similar to that used in patients. Two cubic centimeters of anesthetic in oil were injected into four intercostal spaces. This is a large quantity in relation to the thin intercostal spaces in dogs. The depth of the site of the injection was more difficult to control in the animals than in human beings. Since we were primarily interested in the early reaction of this material, the animals were sacrificed one, two, seven, and fourteen days after the injection. Further studies on the effect of this material are in progress.

Invariably there was a noticeable reaction about the pleura in the area injected. Also there was usually a small amount of fluid in the chest and a deposit of fibrin on the surface of the lung opposite the injection. In one animal 8 c.c. of eucupin solution in oil were injected directly into the pleural cavity, and the animal was sacrificed after one week. At autopsy a small amount of thin, brown fluid was found in the chest, a minimal amount of reaction compared to what might have been expected. The accidental injection of eucupin solution in oil directly into the pleural space in patients would probably be without consequence.

#### RESULTS

Like any attempt at infiltration anesthesia, the results are not uniformly successful. This can be expected, especially if a small amount of solution is injected. Furthermore, as previously stated, it is difficult to evaluate in some patients the amount of discomfort after operation. Some nervous, apprehensive individuals, despite the fact that they did not require much sedation for relief of their pain, did not cooperate when vital capacity determinations were made.

For purposes of analysis we have divided the instances in which eucupin solution in oil was used as an intercostal nerve block into two groups: biliary operations and gastric resections. The former group was made up of 10 women, in 8 of whom choledochostomy in addition to cholecystectomy was carried out. In 9 the block included the sixth

to the eleventh intercostal space in the midaxillary line on the right side. Only in 1 patient was a bilateral block produced.

Fig. 4 presents the vital capacities of these patients before operation and on the four days immediately following operation contrasted to those of 48 women on whom similar operations were carried out without intercostal block anesthesia. The majority of the patients had a vital capacity greater than the median vital capacity attained by any 1 of the 48 in the control group. The vital capacity of 1 female quite remarkably was not below 3,000 c.c. after operation. Six of the 10 were above the maximum on the first postoperative day, while 1 equalled the maximum and 3 were below.

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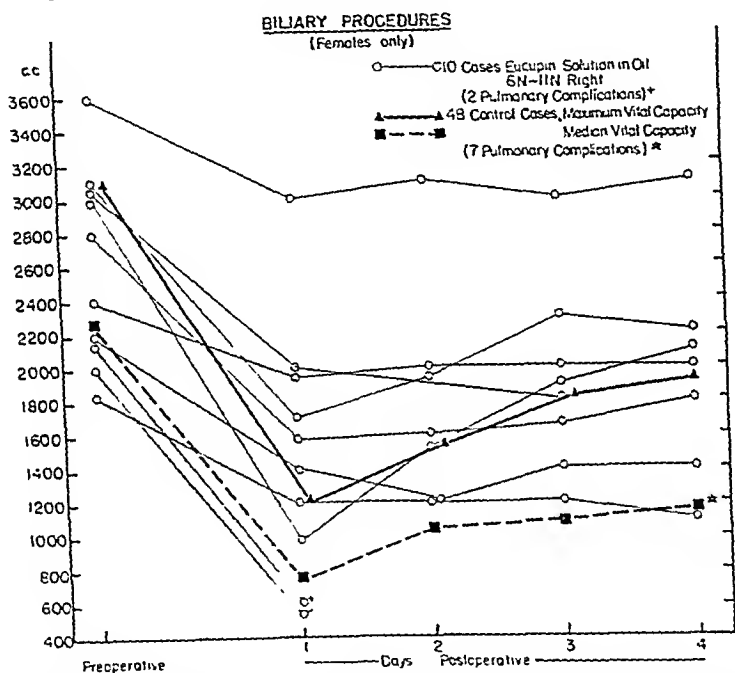


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An x-ray of the chest, taken eight days after operation in the patient with bilateral block, showed fairly marked clouding, together with some fluid at the right base but no displacement of the heart or trachea. The left side was clear. A diagnosis of bronchopneumonia and pleural

effusion on the right side was made. She had a sustained elevation in temperature for two weeks, which gradually returned to normal.

An x-ray of the chest of the second patient on the third day after operation showed clouding of the right base, suggesting a small amount of fluid obscuring the diaphragm and costophrenic angle. The lungs elsewhere were clear. This patient's recovery was not interrupted, and she was discharged on the thirteenth day after operation.

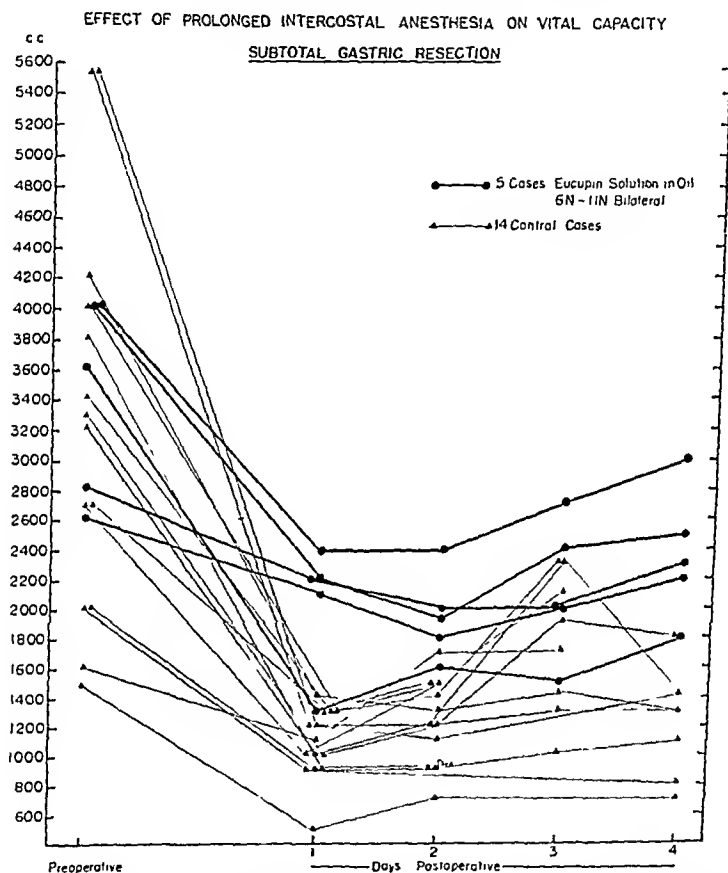


Fig. 5.—Comparison of vital capacities of 14 control cases before and after gastric resection with 5 cases in which eucupin solution in oil was injected intercostally on both sides.

The question may be raised of whether or not the eucupin solution in oil was accidentally injected into the chest. It is our opinion that the intercostal nerve block was not primarily responsible for the patients' pulmonary complications. Obviously, we cannot say that we have been able to decrease the incidence of pulmonary complications in this small series of cases; although it is admittedly true that these two patients who developed pulmonary complications did not have a satisfactory block, as shown by their evident distress immediately after operation.

Fig. 5 is a comparison of 5 patients submitted to subtotal gastric resection, when eucupin solution in oil was injected bilaterally to produce intercostal block, with 14 in which it was not used. The majority of these were men. In general, it is difficult to compare the vital capacity readings of men and women. While the readings of the men may be as low as those of the women on the first day, the former return to normal much more rapidly. As shown in the chart, the vital capacity in the control cases was abruptly lowered to 1,400 c.c. or below, regardless of the preoperative reading, which in two instances was as much as 5,500 c.c. There was some increase on the second postoperative day, and a sustained increase on the third day. In 4 of the 5 patients with nerve block, the fall of the postoperative vital capacity was not nearly so marked and the vital capacity readings averaged from 2,100 to 2,400 c.c. There was some evidence that the anesthesia was not as effective on the second day, in that the vital capacity showed a trend to a lower level then, followed by a sustained rise. One patient after radical resection of the Polya type, including fundusectomy, showed a vital capacity on the first two postoperative days comparable to the maximum for the control group. There were no pulmonary complications in the patients in whom the block was used, while there were five in the control group. At least 2 of the patients having gastric resection had no morphine after operation.

If the patient has a decrease in the usual distress in the wound following operation, as shown by an increase in vital capacity, one should be able to demonstrate persistent anesthesia of the abdominal wall. In a few patients we found a spotty, persistent anesthesia the day following operation, but in the majority sensation had returned to the skin in the blocked area by the time of the testing. Despite the lack of local anesthesia, the patients did not have any significant amount of pain. This observation coincides with that of de Takats, who has pointed out that with eucupin injection a prolonged period of analgesia follows the period of local anesthesia.

One patient who complained of pain on the first day after operation stated that the pain was located in the left epigastrium below the lower angle of the incision outside the zone supplied by the block. This "migration of pain" after anesthetization of a painful area has been described by Weiss and Davis, who suggested that after alleviation of pain by local infiltration of the skin with novocain, the pain may recur in a corresponding segment which is more sensitive. The observer must be aware of this possible manifestation of referred pain.

Whether or not these patients will show evidence of a chemical neuritis or an intercostal neuralgia, as sometimes follows paravertebral alcohol injection, remains to be seen. Only 2 patients of the entire group have complained of any discomfort at the point of injection and this was not particularly noteworthy.

Although the number of patients here reported having intercostal nerve block with an anesthetic in oil is small, the method seems to be of value when one considers the marked elevation in vital capacity during the early days after operation in the majority of instances. Whether the lower incidence of pulmonary complications is real or fortuitous remains to be seen. Clinically, and particularly from the point of view of the patient, the procedure appears to be worth while. Further investigations are in progress.

#### CONCLUSIONS

1. The block of the sixth to the eleventh intercostal nerves with eucupin solution in oil decreases the postoperative pain of upper abdominal incisions, as demonstrated by vital capacity measurement.
2. The question of whether intercostal nerve block with eucupin solution in oil will decrease the incidence of postoperative pulmonary complications can be answered only by further observations in a larger series of cases. The procedure seems to have merit and warrants further investigation and clinical trial.

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## BENIGN STRICTURE OF THE BILE DUCTS TREATED WITH A VITALLIUM TUBE

HERMAN E. PEARSE, M.D., ROCHESTER, N. Y.

*(From the Department of Surgery, the University of Rochester  
School of Medicine and Dentistry)*

**B**ENIGN strictures of the bile ducts may follow injury during cholecystectomy, ulcerations from stones, or septic cholangitis. They are always a difficult situation to manage and if very extensive may present an insoluble problem. Two general principles have been used in their operative repair; either an attempt to restore the lumen of the damaged duct or transplantation of its proximal end into the intestinal tract. Restoration of the duct has been done by (1) dilatation or division of the stricture, (2) plastic repair usually by the Heineke-Mikulicz principle, (3) excision of the stricture with end-to-end anastomosis of the duct, or (4) the use of a rubber tube to bridge the gap between the ends of the duct. These operations have the advantage of retaining the action of the sphincter of Oddi and so prevent ascending infection. If either plastic repair or end-to-end anastomosis of the duct can be done without tension on the suture line, the results are often satisfactory. These are the best procedures for the management of the less severe strictures.

The proximal end of the common or hepatic duct has been transplanted into the stomach, duodenum, or jejunum. An external biliary fistula has been utilized for transplantation into the intestine. Finally, indirect transplantation has been done with a tube from the hepatic duct to the intestine. Of these hepaticoduodenostomy has been the most frequently employed, but all have the possible danger of cholangitis due to infection ascending from the intestinal tract into the biliary system. They also are prone to resticture at the site of the anastomosis.

This report deals with the use of a buried vitallium tube to repair extensive strictures of the ducts. The method was thought of in connection with the patient in Case 1, who on two occasions was perfectly well as long as a T-tube was in the duct but who had stricture formation and a return of symptoms after removal of the tube. The use of a buried tube left in place permanently was an obvious solution if one could be found that was satisfactory. The work on bones and joints had shown that vitallium was practically inert in the tissues probably from absence of electrolysis. It was selected for the purpose\* in the hope that it would

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

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be tolerated well enough to keep the strictured duct patent. When the vitallium tube relieved the symptoms of cholangitis and biliary obstruction in the first patient, we were encouraged to suggest its use in two other patients. These are reported.

CASE 1.—M. T. (No. 151537) was admitted March 29, 1939. This 30-year-old woman had had a cholecystectomy elsewhere in July, 1937. She was told that the common bile duct was explored and that several small stones were removed from it. Recovery was slow and she was in the hospital five weeks. Soon after healing of the wound she began having attacks of epigastric and interscapular pain associated with nausea, vomiting, chills, fever, and jaundice.

A second operation was done elsewhere in May, 1938, at which time she was told a stone was removed from the common bile duct. A catheter drained bile after this operation and she felt perfectly well until after its removal. Then the symptoms of pain, nausea, vomiting, chills, fever, and jaundice returned. Intense itching, clay colored stools, and dark urine were occasionally observed.

In the past she has had five normal pregnancies and a laparotomy four years ago for uterine suspension.

Physical examination revealed a well-developed, moderately well nourished woman with sallow skin, icteric sclerae, three well-healed abdominal scars, and a liver palpable just below the costal margin. All other physical findings were within normal limits.

Laboratory studies gave the following results: *Blood*: R.B.C., 4,200,000; W.B.C., 7,500; Hgb., 12.5 Gm.; differential normal; Wassermann negative; bleeding time, 2½ minutes; clotting time, 3 minutes; prothrombin time, normal; fragility of R.B.C., normal. *Blood Chemistry*: N.P.N., 33; sugar, 70; icterus index, 15; albumin, 2.85 per cent; globulin, 2.87 per cent; total protein, 6.8 per cent; cholesterol, 250 mg. *Urine*: Specific gravity, 1.025; alkaline; albumin, 0; sugar, 0; acetone, 0; guaiac, negative; mic. 3 to 5 W.B.C. per field; foam test, trace of bile; HgCl<sub>2</sub> test negative. Stool guaiac negative, no parasites found. Duodenal drainage shows numerous cholesterol crystals. The glucose tolerance test shows a normal curve. Agglutination of the blood was found in 1:80 dilution of *Brucella abortus* and *Br. melitensis*. No agglutination for *Bacillus typhosis* or *B. paratyphosis*. X-ray of the gall bladder region showed no opaque calculi.

A diagnosis of stricture of the common bile duct with cholangitis was made.

At operation, April 5, 1939, the gastrohepatic ligament was exposed, the portal vein and hepatic artery were isolated from dense scar tissue, but the bile duct could not be found. At this stage a small spot of bile was seen up under the liver and on tracing its source it was found to be coming from a threadlike structure in scar tissue. This was the remnant of the common duct. Traced upward it led to a dilated hepatic duct containing bile under pressure, gravel, and two stones. Below it led to the stump of the common duct which protruded about ¼ inch above the pancreas. The two ends were separated by a gap of about 1½ inches (Fig. 1, 1), but due to unusual mobility of the pancreas and duodenum it was possible to join them by an end-to-end anastomosis over a T-tube (Fig. 1, 1a). Recovery was uneventful.

On May 18, 1939, six weeks after operation, the duct system was visualized by x-ray after injection of opaque media and found to be patent so the T-tube was removed. She was well for three months, but then nausea, vomiting, chills, fever, and jaundice returned. At this time it was found that she was pregnant and when careful regulation failed to influence her symptoms the pregnancy was interrupted for it was an obvious menace to her.

The attacks of cholangitis grew worse in spite of all treatment until she was having a daily chill with temperature of  $40^{\circ}\text{C}$  ( $104^{\circ}\text{F}$ ). It was apparent she could not survive in this condition, yet it was thought that there was too little duct left for further attempts at plastic repair. It was decided to intubate the duct permanently.

On Feb 26, 1940, the fourth operation on the biliary ducts was done. After freeing dense adhesions the dilated stump of the hepatic duct was exposed and a stricture found at the point of former anastomosis (Fig 1, 2). There was one stone

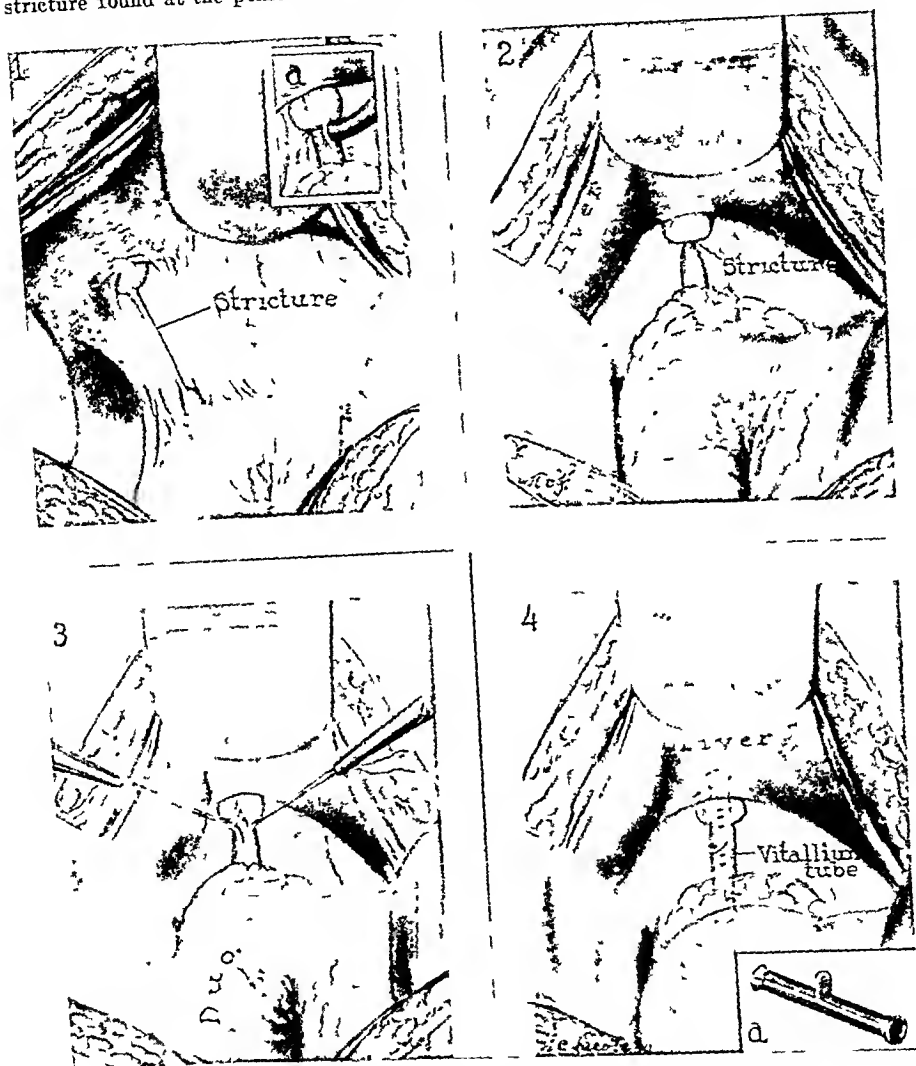


Fig 1—1, The stricture of the bile ducts in Case 1 extended from the upper hepatic duct to the lower common bile duct. For clarity it is shown isolated but in reality it was buried in dense scar tissue since this was the third operation on the biliary tract. a shows the method of repair by end-to-end anastomosis over a T-tube. This was made possible by exceptional mobility of the duodenum and pancreas. 2, Ten months later the anastomosis had strictured down to a small opening but the ends of the duct were held together by scar tissue. 3, The ducts were opened without dividing their attachment to one another. 4, The vitallium tube was slipped into the ducts and their anterior walls were closed over it. The flange protruded through the suture line. a drawing of the vitallium tube showing the thickening of the ends and the central flange which acts as an anchor.

removed from the duct above the stricture. The vitallium tube was inserted into the duct which was closed about it (Fig. 1, 2 and 3). Recovery was uneventful.

Follow-up examinations at monthly intervals for one year have shown the patient to be in good condition. On one occasion she developed indigestion and diarrhea, possibly from too much sodium taurocholate for when this drug was eliminated the symptoms subsided. She is now well.

CASE 2.—B. L. (No. 168083), was admitted Aug. 1, 1940. Two years before this 37-year-old married white woman had had a cholecystectomy at another hospital because of symptoms of right upper quadrant abdominal pain radiating to the back, nausea, vomiting, and jaundice. The wound drained for three months. Six months postoperatively she began having recurrent attacks of right upper quadrant abdominal pain more severe than before the operation. These have been associated with nausea, vomiting, chills, fever, jaundice, clay-colored stools, and dark urine. Recently the jaundice has been constant though it fades somewhat between attacks.

The physical examination, except for jaundice and a healed abdominal scar, was negative. Temperature was 37° C.; the pulse, 80; the respirations, 20; and blood pressure, 120/76. Laboratory examinations showed bile in the urine; clay colored stool; negative Wassermann; blood N.P.N., 34 mg. per cent; sugar, 90; icterus index, 48; amylase, 100; prothrombin time, normal (26 seconds). X-ray examination of the abdomen showed no opaque calculi.

A diagnosis of residual common duct stone or stricture of the common duct was made and operation was advised.

*Operation* (Aug. 5, 1940, Dr. T. B. Jones).—The abdomen was opened through an upper right paramedian incision. Numerous adhesions were freed to expose the stomach adherent to the gall bladder bed. There was a broad band of tissue binding the stomach to the region of the cystic duct. When this was divided, bile escaped and a small fistula was demonstrated between the stump of the cystic duct and the stomach. The gastric opening of this was inverted with silk. The hepatic artery was anomalous, being located to the right and posterior to the common duct. The bile duct was a fibrous cord from just distal to the hepatic ducts down to a point 1.5 cm. above the duodenum. The stricture was considered to be too extensive for a satisfactory plastic repair. Consequently a vitallium tube was inserted into the proximal part of the duct just below the bifurcation of the hepatic ducts and was held in place with C silk sutures. The lower part of the tube was sutured in place into the distal end of the common duct. But the two ends of the duct could not be joined over the tube. A cigarette drain was inserted through the right flank into the gall bladder bed some distance from the common duct and the wound of exploration was closed with silk sutures.

The patient made a smooth postoperative recovery. The icterus index was 36 two days after operation and fell to 14 five days later after which the clinical signs of jaundice disappeared. She was discharged from the hospital on the eighteenth postoperative day in good condition.

Follow-up examinations at monthly intervals revealed her condition to be very good until five months after operation at which time she complained of gas, diarrhea, and bulky, "frothy" stools. She had gained 16 kg. in weight and was eating excessively because her appetite was "tremendous." A blood icterus index was 8; cholesterol, 283; and amylase, 160. A low fat diet and sodium taurocholate, 0.5 Gm. b.i.d., was prescribed. Two weeks later, Jan. 22, 1941, she had jaundice with itching of the skin and an icterus index of 24. There was no pain, chills, fever, or vomiting associated with this. On Jan. 29 the jaundice was increased with an icterus index of 36. By Feb. 5 the icterus index was 50 so she was readmitted to the hospital for operation.

*Operation* (Feb. 8, 1941, Dr. H. E. Pearse).—Dense adhesions were freed to expose a strictured stump of the common hepatic duct only 0.5 cm. of which was patent below the bifurcation into the right and left hepatic ducts. A stump of scar tissue protruded from beneath the duodenum, and by tracing this down, a patent common duct was defined. This was confirmed by making a small opening in the duodenum to inspect the ampulla with a probe in place. The vitallium tube had pulled out of the ducts and lay free beneath the pancreas and duodenum.

The two ends of the bile ducts approached one another at an acute angle so that when a T-tube was inserted into them it buckled in the middle. There was so much scar in the stump of the hepatic duct that it appeared probable that a hepaticoduodenostomy would result in stricture formation. Consequently the vitallium tube was reinserted and the ends of the ducts were sutured. The duct ends could only be approximated on their posterior wall by the use of some tension. The flange on the tube protruded between the ends on the anterior surface. The patient stood the operation well and is making a satisfactory recovery.

The following résumé was obtained through the courtesy of Dr. Howard M. Clute, of Boston, who operated upon the patient.

CASE 3.—Mrs. M. L. (No. 2488).

1. Cholecystectomy for gallstones was performed elsewhere sixteen months before. Hemorrhage occurred from the cystic artery. A clamp was hurriedly placed and left in place 24°. It apparently included the uppermost portion of the common duct in its grasp.

2. Common duct was explored four months before elsewhere because of attacks of pain, fever, chills, and jaundice. No stones were found. Stricture was not found.

3. At operation (Dr. Clute) on July 27, 1938, a stricture, almost complete, very high in common duct was found. The stricture was incised longitudinally, and a T-tube drain placed in it. The patient was well for five months with the tube in place. It was then pulled out. Soon after that attacks of pain, chills, fever, and jaundice began again.

4. At operation (Dr. Clute) on April 14, 1939, with great difficulty the strictured common duct was exposed. There was about one-eighth inch of common hepatic duct present. The duodenum was freed, and a hepaticoduodenostomy was done. A ring of fibrous tissue about the common hepatic duct opening made us fearful that the new opening might contract and obstruct. After six or seven months this occurred, and her old attacks of pain, chills, fever, and jaundice returned.

5. At operation (Dr. Clute) on Nov. 29, 1940, the common duct was again exposed and the duodenum was cut free from its anastomosis to the common hepatic duct. The anastomosis had diminished to pin-point size. The opening in the duodenum was closed. The common hepatic duct was now found lying somewhat in liver tissue and consisting really of only a ring of firm fibrous scar tissue. In the duct was much detritus and many tiny black gallstones. The end of the duct was enlarged and the trumpet-shaped end of a vitallium tube was inserted in it (Fig. 2) and held securely with two silk sutures. The distal end of the tube was placed in the common bile duct about one inch of which was absent. A jejunostomy was made for postoperative feeding. Recovery was entirely uneventful, her highest temperature being 99.4° the day after operation.

At last follow-up visit, Jan. 20, 1941, she was entirely well.

DISCUSSION

The literature has been studied, but it does not appear necessary to review it here. Those interested will find that Kehr<sup>1</sup> reports the earlier

work and that the review of Eliot<sup>2</sup> gives a good bibliography of recent articles on the subject.

The implantation of a buried tube to repair strictures of the bile ducts is not new for it has been used to bridge temporarily an irreparable gap or to hold open an anastomosis. These tubes were tied in place in the hope that they would loosen and pass spontaneously after restoration of the duct. When the use of a permanently buried tube was first considered, it was thought that rubber would be unsatisfactory for it



Fig. 2.—A vitallium tube in place in the bile ducts shown in relation to the stomach which is filled with barium. The bell-shaped upper end was used by Dr. Clute in Case 3 to collect bile from the right and left hepatic ducts for the patient's stricture was just below their bifurcation. A Y-shaped tube has also been suggested for this purpose.

would rot. Judd<sup>3</sup> reports a case of a rubber tube being in place for six years and Brooks<sup>4</sup> tells me of a case of his with a T-tube still in the duct after six years. Yet these are exceptions to the general rule that rubber begins to deteriorate in a year or so.

Vitallium has been shown<sup>5, 6</sup> to be the best tolerated of any metal in the tissues. It was also thought to be superior to glass or a plastic. The strength, lack of electrolysis, and lack of tissue irritation, all recommend vitallium for this purpose. The tubes were made with an internal



diameter of 5 mm. and a length of 4 cm. The ends were flared slightly to give added thickness at the edge to prevent pressure erosion. A flange was put in the center as an anchor. This protrudes through the wall of the duct and prevents the tube from slipping up or down. There have been several modifications of the anchoring device suggested, but so far none have appeared better than this simple flange. In Case 3 Clute wanted a tube to drain the two hepatic ducts for the patient had a high stricture. He obtained a Y-shaped tube and also one with a bell-shaped dilatation of one end. The latter was used and is shown in Fig. 2.

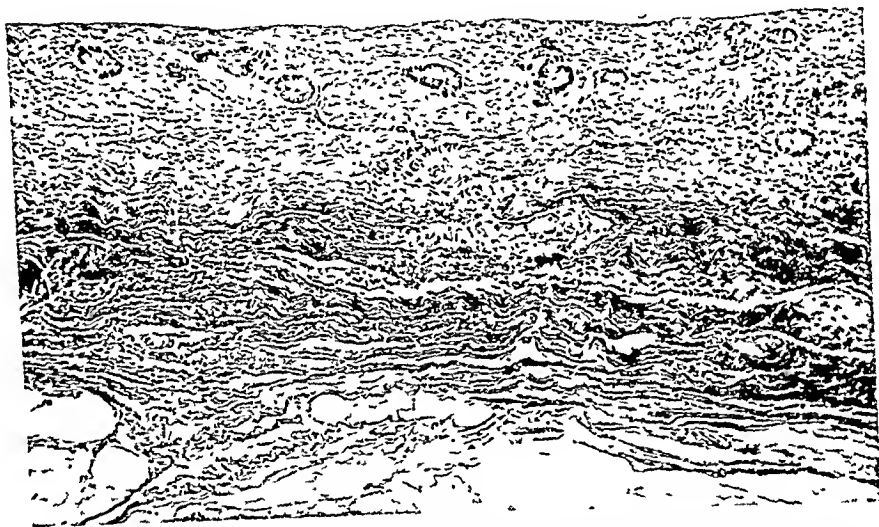


Fig. 3—A vitallium tube has been in this dog's common bile duct for two months. The suction shows little change in the mucosal lining or in the wall of the duct.

It is felt that these tubes of vitallium should only be used in extensive biliary strictures which appear irreparable by other means for the hazards of this permanent intubation of the ducts cannot now be fully estimated. The patient in Case 1 has gone one year after operation without difficulty. Experiments in dogs have shown that the tube remains patent for months, the metal retains its luster, there is no deposition of pigment or salts on it, and the mucosa lining the duct is not seriously eroded (Fig. 3). But these experiments are only of a few months' duration and it will require years for the final answer. The same is true of experiments to test the effect of bile on the metal. Dr. Robert Sewell in our laboratory has had strips of vitallium suspended in human bile for several months without any indication of erosion of the metal.

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## ADHESIONS FROM HOT LAPAROTOMY PADS

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THE proper temperature for moist laparotomy pads applied to the abdominal viscera has not been extensively studied. Most writers have urged that they be kept warm enough to avoid cooling the peritoneum. A cursory search through the voluminous literature on adhesions revealed that only Lamson<sup>1, 2</sup> and Benjamin<sup>3</sup> have mentioned the obvious fact that excessively hot pads may injure the peritoneum and cause postoperative adhesions. Since it is a common occurrence for the surgeon to be handed a pad that is literally too hot to handle, a more careful study is indicated of temperatures that cause thermal injury to the serosa.

### MATERIAL AND METHODS

The effect of hot laparotomy pads on the peritoneum was studied in a series of twenty-six dogs. After laparotomy through a rectus incision several feet of small intestine, a portion of omentum, and in some cases the spleen were delivered into the wound. Pads were removed from large beakers of sterile water at known temperature, wrung out, and applied to these viscera for at least two minutes. Care was taken to keep drying and mechanical trauma at a minimum. The wounds were closed and the animals were sacrificed after intervals of two to forty-nine days postoperatively.

At post-mortem the viscera subjected to hot laparotomy pads were examined for the presence of adhesions. Microscopic studies were made of involved areas. An attempt was made in other experiments to determine the thermal death point of serosal cells in spread preparations of omentum and mesentery supravitaly stained with neutral red and methylene blue. In another study a comparison was made between the temperature of moist laparotomy pads and the sensation induced in the surgeon holding these pads in his gloved hands.

### GROSS FINDINGS

The effect of hot laparotomy pads on the production of adhesions in 26 dogs is summarized in Table I. In the case of 5 control animals in which the pads were applied at approximately body temperature (35 to 40° C.) no adhesions were present. In 6 dogs after laparotomy pads at 45° C., 1 had no peritoneal injury, 4 had moderate and 1 marked

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It would appear likely that the greatest value of permanent implantation of a vitallium tube into the bile ducts will be to hold open a strictured area such as existed in Case 1. Its value is problematical if a gap is to be bridged between the ends of the duct. Here the tube may slip out as happened in Case 2. In such a situation it may be possible to free the duodenum and pancreas in order to gain mobility of the distal end of the common duct. The duodenum, pancreas, and duct could then be brought up near the hepatic duct. This was suggested by Dr. Earle Mahoney and was attempted at our second operation in Case 2 but was only partially successful due to scar tissue binding the under-surface of the pancreas. Normally there exists a good cleavage plane which might permit this maneuver.

The real test of the vitallium tube will be its use in clinical cases of severe biliary stricture which have not been corrected by previous operations. Here the surgeon has little to offer the patient so the prospect of benefit from the tube is sufficient to warrant its trial.\*

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\*The cases reported above have remained well to date (June 14, 1941). Other cases have been operated upon, here and elsewhere, with satisfactory results confirming the conclusions drawn in this report.

Supravital studies on freshly excised omentum and mesentery stretched over a cork ring showed that an exposure of two minutes at  $50^{\circ}$  killed some and  $55^{\circ}$  killed most of the mesothelial cells lining the serosa. This immediate damage to the cells occurred whether the thermal injury was applied by means of hot pads before excision or by immersion in Locke solution after excision.

#### PERCEPTION OF TEMPERATURE

During operation the surgeon is handicapped in perceiving the approximate temperature of moist laparotomy pads because of the insulating effect of rubber gloves. A pad at  $45^{\circ}$  C. does not feel warm at all, unless compressed in the cupped hands for some time. A pad at  $50^{\circ}$  feels comfortably warm after being held for about fifteen seconds. A pad at  $55^{\circ}$  is noted to be hot after five seconds but can be held indefinitely without discomfort. Only above  $55^{\circ}$  are painful sensations produced. The perception of heat is more rapid and more accurate when the gloved hand is immersed in the water, since the area of contact is greater and there is no cooling of the water during the period of observation. With immersion  $50^{\circ}$  is felt as warm in five seconds, while  $55^{\circ}$  is perceived as hot in three seconds and becomes somewhat uncomfortable in about fifteen seconds. Therefore either method of testing the temperature with the gloved hand is not accurate enough to avoid the use of pads that may cause thermal injury to the serosa. A pad that feels hot to the surgeon is too hot for the delicate peritoneum by some 5 or  $10^{\circ}$  C.

#### DISCUSSION

Since hot moist laparotomy pads under the conditions of these experiments caused severe damage to the peritoneum, the question should be raised whether they are necessary for routine packing and retraction. No studies were found in the literature to support the widely held belief that pads below body temperature are harmful. It seems quite unlikely that moist pads at room temperature cause any local damage to the bowel. It is also questionable that their lower temperature would incite reflex changes or cause enough loss of heat to contribute appreciably to the production of shock. It has been adequately demonstrated that refrigerated blood and saline solution at room temperature can be injected intravenously without harm provided the rate of injection is not excessively rapid. In any case temperatures above  $45^{\circ}$  C. are not necessary to avoid chilling, if the pads are not allowed to become cold before being applied.

Even when warm pads are required in special circumstances, precautions may be observed. In the application of a warm pack to hasten return of circulation in determining the viability of a loop of intestine after release of a strangulation excessive heat would seem particularly

TABLE I

NUMBER AND DEGREE OF ADHESIONS PRODUCED IN 26 DOGS BY APPLICATION OF HOT LAPAROTOMY PADS

TEMPERATURE (C.)	DOGS	ADHESIONS		
		SLIGHT	MODERATE	MARKED
35-40°	5	0	0	0
45°	6	0	4	1
50°	8	1	1	6
55-65°	7	2	1	4

adhesions. Moderate adhesions consisted of several bands or a single loop firmly adherent. Marked adhesions involved many loops of intestine. Of 8 dogs after laparotomy pads at 50° C., 6 showed massive adhesions, 1 moderate and 1 slight adhesions. After higher temperatures, 55 to 65° C., 4 of 7 dogs had massive adhesions, 1 died of peritonitis, and 2 showed a single adhesive band on the ileum. During operation intense hyperemia and in some cases punctate subserosal hemorrhages were noted to result from excessively hot pads.

The density and firmness of the adhesions varied with their duration and also with the extent of peritoneal damage. The moderate adhesions from 45° pads were largely thin bands while those from 50° and above consisted of broadly approximated bowel-to-bowel adhesions. As early as ten days postoperatively these broad adhesions could scarcely be pulled apart without tearing the bowel wall. Attachment of the omentum to the involved areas was often extensive but rarely firm.

Apparently the omentum and the peritoneal suture line were the only structures to take part in the formation of adhesions regardless of their exposure to hot pads. The parietal peritoneum and other portions of the gastrointestinal tract not subjected to thermal trauma did not become involved. Hot pads to the spleen produced fibrinous and fibrous thickening on its surface, omental attachments, but no adhesions to the neighboring stomach, colon, or parietal peritoneum.

#### MICROSCOPIC OBSERVATIONS

Sections revealed that destruction of serosa, with one exception, was relatively slight after 45° pads. These adhesions, therefore, tended to become stretched out into thin bands. After 50° or more the small intestine was extensively denuded of serosa and the subserosal tissues became attached to other raw areas or to omentum. An intense fibroblastic response took place in these adherent loops of bowel, which extended in some cases deep into the muscularis. Fibrous replacement began in about two weeks with little or no tendency for the adhesions to become stretched out. When an interposed process of omentum limited the area of attachment between loops of bowel, the bridging of the denuded surfaces by fibrous tissue seemed less marked.

# THE LATE RESULTS IN ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

WITH PARTICULAR REFERENCE TO MULTIPLE ULCER

EDWARD F. PARKER, M.D., CHARLESTON, S. C.

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ACUTE perforated peptic ulcer still constitutes a grave surgical disease, as regards both early and late prognosis. Since advocacy by Mikulicz<sup>1</sup> in 1880 of simple suture, this in general has been the method of treatment most widely used throughout the civilized world.

The first accurate authentic description of an acute perforated ulcer of the duodenum was apparently made by Penada<sup>2</sup> in 1793. Gerard<sup>3</sup> in 1804 cited a case of spontaneous perforation of the duodenum. Thereafter in the first half of the nineteenth century, there are many references to spontaneous perforations of the intestine, in particular of duodenal ulcers. On reading one of them (Bainbridge<sup>4</sup>) one gathers that the condition was well recognized by leading practitioners of the time, and especially by pathologists.

It was not, however, until after the performance by Billroth in 1881 of the first successful partial gastrectomy, and by Wolfer in 1881 of the first gastroenterostomy, that early operations for acute "perforative peritonitis" were first performed. In the earlier cases, all the patients died, and at autopsy there were found perforated peptic ulcers which frequently had been overlooked at operation. Either Huesner<sup>5</sup> or Kriege<sup>6</sup> in 1892 was the first to suture successfully a perforated gastric ulcer, but the original article does not state which of these two actually performed the operation. And Dean<sup>6</sup> in 1894 was probably the first to suture successfully a perforated duodenal ulcer (though the patient died on the nineteenth postoperative day of intestinal obstruction).

The early history of operations for perforated duodenal ulcers up to 1901 is well recorded by Moynihan,<sup>7</sup> who reported 51 cases, including 2 of his own. In a later article on gastric and duodenal ulcers, Moynihan,<sup>8</sup> as in his article on duodenal ulcers alone, again advocated complementary gastroenterostomy in addition to simple suture, if it appeared "that a stricture of the bowel will inevitably result."

While simple suture has been the most widely used method of therapy, others have also been used; namely, simple suture plus gastroenterostomy, excision of the ulcer combined with some type of pyloroplasty, and primary gastric resection. On a review of the literature, there seems still to exist considerable difference of opinion not only as to the

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undesirable, since slowing of circulation increases the susceptibility of tissues to thermal injury. Hot packs are frequently employed for hemostasis in the pelvis, gall bladder region, and splenic bed. If contact of such hot packs with the jejunum and ileum is avoided, the likelihood of troublesome adhesions is minimized. The temperature that will most effectively control capillary oozing is above the threshold of thermal injury to the serosa.

#### SUMMARY

In a series of dogs hot moist laparotomy pads caused injury to the peritoneum and postoperative adhesions. Temperatures of 50° C. (122° F.) for two minutes caused severe damage to the serosa of the small intestine. Some evidence of thermal injury occurred at 45° C.

It is concluded that hot laparotomy pads, except for hemostasis, are unnecessary, harmful, and may play a role in the formation of post-operative peritoneal adhesions in man.

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method of choice, but also as to the beneficial results to be obtained from any given method.

The purpose of this article is to report a study of the late results of the treatment of acute perforated peptic ulcer by simple suture; to review the literature on the late results of its treatment by this and other methods; and to point out the frequent high incidence of multiple peptic ulcer.

#### MATERIAL

From 1921 through 1938 there were admitted to the Roper Hospital 52 cases of acute perforated peptic ulcer treated by immediate operation. Of these cases, 25 survived, while 27 died, a mortality rate of 52 per cent. Of the 25 patients who survived, we have been able to obtain satisfactory follow-up studies in 18.

The 18 cases (see Table I) followed were operated upon by a number of different surgeons. In all of the 18 cases, the treatment was immediate operation with simple suture. However it is to be noted that in 5 of the 18 cases, other procedures in addition to simple suture were performed. In Case 3, the ulcer was "cauterized" preliminary to simple suture. In Case 5, the ulcer was "cauterized with the actual cautery" preliminary to simple suture at the primary operation. In Case 6, the ulcer was "cauterized with the actual cautery" and associated appendectomy was also performed. In Case 7, the ulcer was "cauterized with iodine" preliminary to simple suture. In Case 10, the ulcer was "cauterized and excised with the actual cautery" preliminary to simple suture.

In this series, there were no cases treated by excision of the ulcer plus pyloroplasty, by simple suture plus gastroenterostomy, or by primary partial gastrectomy.

The purpose of the data, gathered on these 18 patients, was to determine the late results of the primary operation. In each case, the patients were personally interviewed and examined by the author, except those cases who had had readmission to the hospital subsequent to the primary operation, and were found "not well" at that time. All cases classified as "well" had recent examination. In no case was a questionnaire resorted to. The late results of any secondary operations performed on any of the patients were not determined.

The late result of the primary operation in each case is classified either as "well" or "not well." In reviewing the literature, the classification of the late results as given by other authors is anything but uniform. In this series, by the term "well," it is meant that the patient considered himself well, able to work with freedom from pain and vomiting, that little or no care had to be taken regarding the diet, and that roentgenologic examination of the stomach and duodenum after a barium meal showed no evidence of an active peptic ulcer. (In one of

the 6 cases classified as "well," a roentgenologic examination could not be obtained.) By the term "not well," it is meant that the patient continued to have, or had at some time subsequent to the primary operation, symptoms which could be attributed to the persistence or recurrence of a peptic ulcer or complications therefrom. In all of the 18 cases, save 2, the presence or absence of a peptic ulcer or complications such as pyloric obstruction was proved at subsequent operation, autopsy, or roentgenologic examination. (In 1 of the 12 cases classified as "not well," the roentgenologic examination was refused, and the diagnosis was made on what was considered indisputable clinical evidence.)

The site of the ulcer at the primary operation was gastric in 4 cases, pyloric in 5 cases, and duodenal in 9 cases. These were the sites as recorded, but in several cases it was stated in the record, as is well known, that the exact localization was difficult to determine due to the presence of a fibrinous exudate on the serosa about the ulcer, obscuring the pyloric vein. In this series, all of the ulcers were on the anterior wall of the stomach, pylorus, or duodenum. In no case were multiple ulcers observed at operation.

Of the 18 cases followed in order to determine the late results of the primary operation, 6 cases, or 33 per cent, were found to be "well" and 12 cases, or 67 per cent, were found "not well," after varying periods of time elapsed following the primary operation. The duration of time since the primary operation for which the cases classed as "well" were followed was 9, 6, 4, 2½ years, and 1 year. In the "not well" cases, the time followed varied from 7 months to 8 years.

Six of the 18 cases, or 33 per cent, were subjected to secondary operation. Three of the 6 cases required immediate secondary operation for a subsequent acute perforation. In these 3 cases, the second perforation occurred from 1 to 5 years following the primary perforation. Thus, 3 of the 18 cases, or 17 per cent, had a second perforation. The other 3 secondary operations were gastroenterostomies. In 1 case, gastroenterostomy was performed for pyloric obstruction two years following the primary operation. In the other 2 cases gastroenterostomy was performed for the persistence of symptoms 1 year, and 2 years following the primary operation.

With full realization of the small number of patients in the series, an attempt was made to determine any possible relationship between patients remaining well or having persistence or recurrence of symptoms, and the following factors: age, race, duration of ulcer symptoms prior to primary operation, duration of primary perforation prior to closure, the site of the ulcer, the size of the ulcer, the use of drainage at the primary operation, complications of the primary operation, and the diet and occupation after the primary operation.

In the cases followed, the ages of the 6 patients who remained well following the primary operation varied from 23 to 48 years, while the

SUMMARY OF PATIENTS WITH ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

TABLE 1

CASE NO.	UNIT NO.	AGE	SEX	RACE	DURATION OF ULCER SYMPTOMS PRIOR TO PERFORATION	DATE OF OPERATION	SITE OF ULCER	SECONDARY OPERATION	DATE OF LAST FOLLOW-UP	SYMPTOMS	GASTROINTESTINAL SERIES	REMARKS	TIME FOLLOWED	LATE RESULT OF PRIMARY OPERATION
1	15391	26	M	W	2 yr.	3/11/29	Duodenal	Simple suture of perforated duodenal ulcer 12/14/34	December, 1934	Recurrent acute perforation		Recovery but no follow-up since secondary operation for reperforation	5 yr.	Not well
2	30711	35	M	C	2 yr.	12/18/30	Pyloric	Gastroenterostomy 7/5/32	July, 1932	Symptoms and signs of pyloric obstruction		Died 1939 of cerebral hemorrhage; history since second operation not known; no autopsy	2 yr.	Not well
3	62090	36	M	W	10 yr.	11/18/31	Duodenal	No	June, 1940	"Gas on stomach," after drinking beer excessively	No evidence of active ulcer	Ulcer "cauterized" at time of closure	9 yr.	Well
4	65095	38	M	W	4 yr.	7/20/32	Pyloric	No	July, 1940	Abdominal pains before and after meals	Active pyloric ulcer	Patient says he has been unable to work because of stomach trouble	8 yr.	Not well
5	65815	53	M	W	59 yr.	4/8/32	Gastric	Gastroenterostomy 11/28/33	November, 1933	Abdominal pain and melena	Deformed pylorus and duodenum	Ulcer cauterized with "actual cautery," at primary operation; "old ulcer," healed at second operation; died 1935 of malaria; no autopsy	18 mo.	Not well

6	68908	24	M	W	1 yr.	7 hr.	11/30/32	Duodenal	Gastroenterostomy 1/30/34	June, 1940	None since secondary operation	Normally function- ing gas- troenter- ostomy	Ulcer cauterized with "actual can- tery," and associ- ated appendec- tomy at primary operation; sec- ondary operation for persistence of symptoms and not pyloric obstruc- tion	8 yr.	Not well
7	78713	41	M	W	3 wk.	6½ hr.	11/ 9/34	Duodenal	No	May, 1940	Occasional gas; no pain	No evi- dence of active ulcer	Ulcer cauterized with iodine; pa- tient has consid- ered himself well	6 yr.	Well
8	81301	51	M	C	3 yr.	7 hr.	5/ 4/35	Pyloric	Simple su- ture perfor- ated gas- tric ulcer 5/23/36	Janu- ary, 1938	Persistent ulcer symptoms	Active duodenal ulcer	At secondary oper- ation site of pre- vious perforation not located	3 yr.	Not well
9	84314	25	M	C	2½ mo.	11 hr.	12/10/35	Pyloric	No	July, 1940	Severe pain and hemi- tonesis	Refused	Intermittent symp- toms since perfor- ation; reopera- tion refused	5 yr.	Not well
10	89118	48	M	W	"Long time"		10/13/36	Gastric	No	May, 1940	No symp- toms	No evi- dence of active ulcer	Ulcer cauterized and excised with "ac- tual cautery," at primary operation	4 yr.	Well
11	92125	47	M	C	11 yr.	6 hr.	4/ 8/37	Duodenal	Simple su- ture perfor- ated duo- denal ulcer 8/9/39	August, 1939	Recurrent nausea per- foration		Recovery from sec- ondary operation; died October, 1939, of unrelied empyem; nu- topsy; multiple duodenal ulcers	2 yr.	Not well

TABLE I  
SUMMARY OF PATIENTS WITH ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

CASE NO.	UNIT NO.	AGE	SEX	RACE	DURATION OF ULCER SYMPTOMS PRIOR TO PERFORATION	DURATION OF PERFORATION PRIOR TO SUTURE	DATE OF OPERATION	SITE OF ULCER	SECONDARY OPERATION	DATE OF LAST FOLLOW-UP	SYMPTOMS	GASTROINTESTINAL SERIES	REMARKS	TIME FOLLOVED	LATE RESULT OF PRIMARY OPERATION
1	1530	26	M	W	2 yr.	26 hr.	3/11/39	Duodenal	Simple suture of perforated duodenal ulcer 12/14/34	December, 1934	Recurrent acute perforation		Recovery but no follow-up since secondary operation for reoperation	5 yr.	Not well
2	36711	35	M	C	2 yr.	15 hr.	12/18/30	Pyloric	Gastroenterostomy 7/5/32	July, 1932	Symptoms and signs of pyloric obstruction		Died 1939 of cerebral hemorrhage; history since second operation not known; no autopsy	2 yr.	Not well
3	62090	36	M	W	10 yr.	6 hr.	11/18/31	Duodenal	No	June, 1940	"Gas on stomach," after drinking beer excessively	No evidence of active ulcer	Ulcer "cauterized" at time of closure	9 yr.	Well
4	67095	18	M	W	4 yr.	18 hr.	7/20/32	Pyloric	No	July, 1940	Abdominal pains before and after meals	Active pyloric ulcer	Patient says he has been unable to work because of stomach trouble	8 yr.	Not well
5	65810	50	M	W	89 yr.	3 hr.	4/8/32	Gastric	Gastroenterostomy 11/28/33	November, 1933	Abdominal pain and melena	Deformed pylorus and duodenum	Ulcer cauterized with "actual cautery," at primary operation; "old ulcer" healed at second operation; died 1935 of malaria; no autopsy	18 mo.	Not well

ages of the 12 patients who did not remain well following the primary operation varied from 18 to 53 years. Thus it did not appear that age was a factor in the late result.

All of the 18 patients followed were males.

Seven of the 18 patients followed were negro. Of these 7, only 1 remained well. The other 11 patients followed were white, and of these 5 remained well while 6 did not.

In the 6 patients who remained well, the duration of ulcer symptoms prior to perforation varied from 3 weeks to 10 years. In the 12 who did not remain well, the duration of ulcer symptoms varied from 3 weeks to 11 years, and 1 of these 12 patients who did not remain well gave no history of ulcer symptoms whatever prior to perforation. Thus it did not appear that the duration of ulcer symptoms prior to perforation was a factor in the late result.

In 5 of the 6 patients remaining well in whom the duration of perforation prior to primary closure was known, the duration varied from 3 to 9 hours, with an average of 6 hours. In the 12 patients not remaining well, the duration varied from 3 to 26 hours, averaging 10 hours. This difference did not appear to be a significant factor in the late result.

The site of the ulcer at the primary operation did not appear to be a factor in the late result. In Table II is shown the site of the ulcer in those remaining well and in those not remaining so.

TABLE II  
SITE OF ULCER IN RELATION TO LATE RESULT

	CASES WELL	CASES NOT WELL
Gastric	2	2
Pyloric	1	4
Duodenal	3	6

In 9 of the 18 cases in which it was stated, the size of the ulcer at the primary operation varied from 1 to 3 cm. in diameter, and did not appear to be a factor in the late result.

Drainage at the primary operation was instituted in all but 5 of the 18 cases, and did not appear to be a factor in the late result.

Complications of the primary operation occurred in 8 of the 18 cases. In 5 of the 8 cases, infection of the wound occurred; in another, disruption of the wound; in another, a pelvic abscess; and in the other a sub-diaphragmatic abscess followed by a peritoneopleurobronchial fistula. Of the 8 cases complicated, only 1 remained well—the 1 complicated by a pelvic abscess. In the 10 cases uncomplicated, 5 remained well and 5 did not. Even so, complications of the primary operation did not appear to be a factor in the late result.

In 11 of the 18 cases in which it was recorded or ascertained, 7 patients followed a diet and 4 followed no diet after the discharge from

TABLE I—Cont'd

CASE NO.	UNIT NO.	AGE	SEX	RACE	DURATION OF ULCER SYMPTOMS PRIOR TO OPERATION	DATE OF OPERATION	SITE OF ULCER	SECONDARY OPERATION	DATE OF LAST FOLLOW-UP	SYMPTOMS	GASTROINTESTINAL SERIES	REMARKS	TIME FOLLOWED	LATE RESULT OF PRIMARY OPERATION
12	92777	23	M	W	3 wk.	5/18/37	Duodenal	No	December, 1937	Recurrence of symptoms	Active duodenal ulcer		7 mo.	Not well
13	97162	35	M	W	2 yr.	3/19/38	Gastric	No	August, 1940	Occasional "gas and heartburn," but nothing like preoperative symptoms	No evidence of active ulcer		2 1/2 yr.	Well
14	98582	32	M	C	2 yr.	6/16/38	Gastric	No	June, 1940	Recurrence of symptoms and tarry stools	Active duodenal ulcer	Well until 1 mo. ago	2 yr.	Not well
15	101110	25	M	W	1 1/2 wk.	11/30/38	Pyloric	No	May, 1940	None	Healed duodenal ulcer		18 mo.	Well
16	101731	12	M	W	8 yr.	12/20/38	Duodenal	No	June, 1940	Cannot eat anything because of pain	Active duodenal ulcer		17 mo.	Not well
17	104453	45	M	C	6 yr.	6/7/39	Duodenal	No	July, 1940	None			1 yr.	Well
18	104712	29	M	C	None	6/25/39	Duodenal	No	May, 1940	Epigastric pain for past month	Active duodenal ulcer		1 yr.	Not well



troubles; and having dyspepsia. Various further examples of the lack of uniformity in classification of the reported late results could be given at length.

Suffice it to say that for the purpose of making comparable the reports in the literature and the report of this series, all of the previously reported late results have been reclassified by the author, into two groups, "well" and "not well." For instance, in the case of one of the examples cited above, those classified as cured are reclassified in this article as "well," and those classified as having grave troubles and having dyspepsia are reclassified in this article in the single group of "not well." In other words, those reclassified as "well" in this article are the patients reported as those considering themselves well, free of stomach trouble, able to carry on their usual work with freedom from pain and vomiting, and having to exercise little or no care regarding their diet. All others are reclassified as "not well."

Only those previous reports are cited in the foregoing tables in which there are definitely stated in the original article by the author, the site of the ulcer at the primary operation, the type of operation performed in each case, the time followed after operation, and in which it was considered satisfactory criteria for study of late results were used, in particular reference to the exclusion of those series in which the

TABLE III

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCER TREATED BY SIMPLE SUTURE

AUTHOR	YEAR RE-PORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL	NO. OF ALL FOLLOWED CASES HAVING REOPERATION
Brown <sup>9</sup>	1925	26	16 (60%)	10 (40%)	
Mills <sup>10</sup>	1925	7	1 (14%)	6 (86%)	1 (14%)
Platou <sup>11</sup>	1929	25	6 (24%)	19 (76%)	11 (44%)
Urrutia <sup>12</sup>	1929	22	11 (50%)	11 (50%)	5 (23%)
Dineen <sup>13</sup>	1929	95	77 (81%)	18 (19%)	10 (11%)
Bryce <sup>14</sup>	1930	100	32 (32%)	68 (68%)	15 (15%)
Hinton <sup>15</sup>	1931	43	23 (53%)	20 (47%)	8 (18%)
White and Patterson <sup>16</sup>	1931	19*	13 (68%)	6 (32%)	2 (10%)
Shelley <sup>17</sup>	1932	29	15 (51%)	14 (49%)	
Gilmore and Saint <sup>18</sup>	1932	44	17 (40%)	27 (60%)	
Scotson <sup>19</sup>	1933	63*	25 (40%)	38 (60%)	
Rousselins <sup>20</sup>	1933	27	12 (44%)	15 (56%)	5 (19%)
Calvet <sup>21</sup>	1935	15	5 (33%)	10 (67%)	5 (33%)
Sallick <sup>22</sup>	1936	45	16 (36%)	29 (64%)	
Guthrie and Sharer <sup>23</sup>	1936	53*	41 (77%)	12 (23%)	10 (19%)
Cabiglio <sup>24</sup>	1936	37	20 (54%)	17 (46%)	7 (19%)
Marin <sup>25</sup>	1936	10	3 (30%)	7 (70%)	
Raven <sup>26</sup>	1936	58*	32 (55%)	26 (45%)	13 (23%)
Cable <sup>27</sup>	1938	24	8 (33%)	16 (67%)	
Eliason and Thigpen <sup>28</sup>	1938	22	15 (70%)	7 (30%)	4 (18%)

\*All duodenal ulcers.

the hospital following the primary operation. The diets followed were of the "soft, bland" variety, and were followed in no case less than two months, and in several cases for as long as a year. Of the 7 patients following a diet, 2 remained well and 5 did not remain so. Of the 4 following no diet, 2 remained well and 2 did not remain so. Thus it would appear that the diet of the variety stated above following the primary operation was not a significant factor in the late result.

The occupation following the primary operation was known in 10 of the 18 cases. Four of the 10 patients remained well; 3 of the 4 did very heavy work, such as stevedoring, while the other was a salesman. Six of the 10 patients did not remain well; 4 of the 6 did heavy work, 1 was a clerk, and 1 was unable to work because of abdominal pain. Thus the occupation following the primary operation was not a factor in the late result.

Six of the 18 patients followed, and therefore 6 (50 per cent) of the 12 patients not remaining well after the primary operation, had secondary operations. Three of the 6 secondary operations were emergency operations for a second perforation. Two of the 3 cases of reoperation were duodenal ulcers at both the primary and secondary operations, while the third was a perforated pyloric ulcer at the primary operation and a perforated gastric ulcer at the secondary operation. The other 3 patients having secondary operation all had gastroenterostomies performed. In 1 case, the gastroenterostomy was performed for pyloric obstruction, while in the other 2, it was performed for persistence of ulcer symptoms. In the 3 patients having gastroenterostomy, the site of the ulcer at the time of the primary operation was 1 gastric, 1 pyloric, and 1 duodenal, in each instance. Thus it would appear that there were no factors of significance relating to the late result as regards secondary operations.

#### REVIEW OF LITERATURE

There have been many reports by various authors of the late results in the treatment of acute perforated peptic ulcer by the different methods which have been used.

The four methods which have been used are simple suture, simple suture with complementary gastroenterostomy, excision of the ulcer with complementary pyloroplasty, and primary gastric resection. The number of reports on the late results by the different methods have appeared in relative frequency in the order named above, as one would expect.

In the various reports, the systems of classification vary considerably. Thus one finds the results classified according to Grades I, II, III, IV. In another, one finds three groups: free of complaint; having symptoms but able to carry on their work on a strict diet; and required reoperation. In another, the cases are reported as: cured; having grave

TABLE VI

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCERS TREATED BY PARTIAL GASTRECTOMY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Paul <sup>35</sup>	1922	11	11	0
Hromada and Newman <sup>36</sup>	1922	13	13	0
Odelberg <sup>37</sup>	1927	8	7	1
Luquet <sup>38</sup>	1936	2	2	0
Mariné <sup>25</sup>	1936	19	19	0

In Table VI are the previously reported late results of the treatment by primary partial gastrectomy, of which there have also been comparatively few. Of a total of 53 cases followed, 52, or 98 per cent, remained well, while only 1 case, or 2 per cent, did not remain well.

## DISCUSSION

From a study of the literature and of the series herein reported it is apparent that the late results of the treatment of acute perforated peptic ulcer are poor, except by primary gastric resection. That is, in those treated by simple suture, it is safe to say that approximately 50 per cent will not remain well, and an appreciable number of these will necessarily have to have some subsequent operation. The late results of the treatment by suture plus gastroenterostomy and by excision plus pyloroplasty as reported are more favorable, but the reasons for this are certainly not clear.

There should be a definite reason for these poor results, and the most likely reason would seem to be the existence of multiple peptic ulcers in an appreciable percentage of the patients presenting the disease of peptic ulcer.

In the series herein reported, some of the patients remained apparently perfectly well until a year or two following the primary operation, only then to have a recurrence of symptoms. Other authors<sup>24</sup> have reported cases in whom the symptoms have recurred as long as five years after the primary operation. In such cases, it seems only logical either that an old ulcer has become active again or that one or more new ulcers have appeared. In this series, one of the patients having two perforations had a pyloric ulcer at the primary operation and a gastric at the secondary. Not included in this series because of death by generalized peritonitis is a recent patient upon whom I operated for perforated duodenal ulcer. At autopsy, there was a duodenal ulcer on the posterior wall, immediately opposite a perforated ulcer on the anterior wall. It is perfectly obvious that this patient would probably have had persistent symptoms even if the anterior wall ulcer healed completely and promptly.

A significant incidence of multiple ulcers, or scars considered to be the result of previous peptic ulceration, is further borne out by a study of pathologic material.

results of questionnaires were used, without personal interviews and examinations of the patients.

In Table III are shown the previously reported late results of the treatment of acute perforated peptic ulcer by simple suture. It is to be noted that the percentage of cases followed remaining well, varied from a high of 86 per cent to a low of 14 per cent. And conversely, of course, the percentage not remaining well varies from a low of 14 per cent to a high of 86 per cent. As an average, of the total number of 764 cases followed, 388, or 51 per cent, remained well, while 376, or 49 per cent, did not remain well. In the reports in which it was recorded, of a total number of 524 cases followed, 96, or 18 per cent, were subjected to secondary operation.

TABLE IV

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCER TREATED BY SUTURE PLUS GASTROENTEROSTOMY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Mills <sup>10</sup>	1925	14	10 (70%)	4 (30%)
Dineen <sup>13</sup>	1929	7	5 (71%)	2 (29%)
Platou <sup>11</sup>	1929	15	15 (100%)	0
Urrutia <sup>12</sup>	1929	12	4 (33%)	8 (67%)
Judine <sup>29</sup>	1929	48	25 (52%)	23 (48%)
White and Patterson <sup>16</sup>	1931	6	4 (67%)	2 (33%)
Shelley <sup>17</sup>	1932	19	16 (84%)	3 (16%)
DeMourges <sup>30</sup>	1932	68	42 (62%)	26 (38%)
Scotson <sup>19</sup>	1933	14	8 (57%)	6 (43%)
Rousseles <sup>20</sup>	1933	3	3 (100%)	0
Marin <sup>25</sup>	1936	30	19 (63%)	11 (27%)
Raven <sup>26</sup>	1936	59	39 (68%)	20 (32%)
Curtillet <sup>31</sup>	1937	12	8 (67%)	4 (33%)
Eliason and Thigpen <sup>28</sup>	1938	21	16 (76%)	5 (24%)

In Table IV are shown the previously reported late results of the treatment by suture plus gastroenterostomy. Here, again there is considerable variation in the number of patients remaining well, varying from a high of 100 per cent to a low of 33 per cent. Of the total number of 328 cases followed, 214, or 65 per cent, remained well, while 114, or 35 per cent, did not remain well.

TABLE V

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCERS TREATED BY EXCISION PLUS PYLOROPLASTY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Rowlands and Turner <sup>32</sup>	1927	12	7	5
Grimault <sup>33</sup>	1929	10	10	0
Williams and Walsh <sup>34</sup>	1930	6	5	1
Hinton <sup>15</sup>	1931	5	1	4

In Table V are shown the previously reported late results of the treatment by excision and pyloroplasty, of which there have been comparatively few. Thus, of a total of 33 cases followed, 23, or 70 per cent, remained well, while 10, or 30 per cent, did not remain well.

TABLE VI

PREVIOUSLY REPORTED LATE RESULTS OF ACUTE PERFORATED PEPTIC ULCERS TREATED BY PARTIAL GASTRECTOMY

AUTHOR	YEAR REPORTED	NO. OF CASES FOLLOWED	NO. OF CASES WELL	NO. OF CASES NOT WELL
Paul <sup>35</sup>	1922	11	11	0
Hromada and Newman <sup>36</sup>	1922	13	13	0
Odelberg <sup>37</sup>	1927	8	7	1
Luquet <sup>38</sup>	1936	2	2	0
Mariné <sup>25</sup>	1936	19	19	0

In Table VI are the previously reported late results of the treatment by primary partial gastrectomy, of which there have also been comparatively few. Of a total of 53 cases followed, 52, or 98 per cent, remained well, while only 1 case, or 2 per cent, did not remain well.

## DISCUSSION

From a study of the literature and of the series herein reported it is apparent that the late results of the treatment of acute perforated peptic ulcer are poor, except by primary gastric resection. That is, in those treated by simple suture, it is safe to say that approximately 50 per cent will not remain well, and an appreciable number of these will necessarily have to have some subsequent operation. The late results of the treatment by suture plus gastroenterostomy and by excision plus pyloroplasty as reported are more favorable, but the reasons for this are certainly not clear.

There should be a definite reason for these poor results, and the most likely reason would seem to be the existence of multiple peptic ulcers in an appreciable percentage of the patients presenting the disease of peptic ulcer.

In the series herein reported, some of the patients remained apparently perfectly well until a year or two following the primary operation, only then to have a recurrence of symptoms. Other authors<sup>24</sup> have reported cases in whom the symptoms have recurred as long as five years after the primary operation. In such cases, it seems only logical either that an old ulcer has become active again or that one or more new ulcers have appeared. In this series, one of the patients having two perforations had a pyloric ulcer at the primary operation and a gastric at the secondary. Not included in this series because of death by generalized peritonitis is a recent patient upon whom I operated for perforated duodenal ulcer. At autopsy, there was a duodenal ulcer on the posterior wall, immediately opposite a perforated ulcer on the anterior wall. It is perfectly obvious that this patient would probably have had persistent symptoms even if the anterior wall ulcer healed completely and promptly.

A significant incidence of multiple ulcers, or scars considered to be the result of previous peptic ulceration, is further borne out by a study of pathologic material.

In the surgical pathologic protocols in the Department of Pathology, we find in 9 stomach specimens resected for peptic ulcer that in 3 of the specimens there were multiple ulcers and/or scars; in one of the 3 specimens there were five ulcers and an old scar; in another there were an old ulcer and an old scar; in the third there were "multiple" ulcers. In an additional 5 specimens consisting of the pyloric end of the stomach and the first portion of the duodenum, the ulcers were solitary. In an additional duodenum specimen, there were two ulcers. Thus, in a total of 15 specimens observed, multiple ulcers and/or scars occurred in 4 cases (27 per cent).

In a study of the autopsy protocols in the Department of Pathology, peptic ulcer was encountered in 44 cases. These cases consisted of all those patients in whom some complication of an ulcer was the cause of death, and also those in whom peptic ulcer was an incidental finding.

In 27 autopsy cases presenting gastric ulcer alone, multiple ulcers and/or scars occurred in 7. These 7 cases consisted of 1 case of "multiple" ulcers; 3 cases of two ulcers; 1 case of an ulcer and a scar; 1 case of two ulcers of which one was perforated; and 1 case of five ulcers of which one was perforated.

In 3 autopsy cases, combined gastric and duodenal ulcers and/or scars were found. In 1 case there was an ulcer in both the stomach and duodenum; in another an ulcer in the stomach and a scar in the duodenum; and in the third case there were two ulcers in the stomach, one of which was perforated, and a scar in the duodenum.

In 1 autopsy case, there were two gastric ulcers, one pyloric ulcer, and one duodenal ulcer.

In 1 autopsy case, there was a single pyloric ulcer.

In 12 autopsy cases presenting duodenal ulcer alone, multiple ulcers and/or scars were present in 5 cases. These 5 cases consisted of 2 cases of an ulcer and a scar; 1 case of "multiple" ulcers of which one was perforated; and 2 cases of an ulcer on both the anterior and the posterior walls, the anterior wall ulcer being perforated in each case.

Thus, in a total of 44 autopsy cases presenting peptic ulcer, there were multiple ulcers and/or scars in 16 cases, or 36 per cent.

In the 44 autopsy cases, perforation of an ulcer had occurred in 11 cases. In these 11 cases, the incidence of multiple ulcers and/or scars was even higher, being 55 per cent (6 of 11 cases).

And, considering the combined autopsy and surgical pathologic material, in a total of 59 cases, multiple ulcers and/or scars occurred in 20, or an incidence of 34 per cent.

The frequent existence of multiple peptic ulcer is by no means unknown. Dunbar<sup>39</sup> stated that "when perforation had occurred at the duodenum, and when a post mortem was obtained, a large proportion showed a second ulcer nearly always opposite the perforation." Luquet<sup>38</sup> remarks on "kissing ulcers." Lewisohn<sup>40</sup> stated that in about 50 per

cent of patients with duodenal ulcer, two or more ulcers were found in specimens after partial gastrectomy.

Graves,<sup>41</sup> in a review of the German literature on peptic ulcer, stated that the high incidence of multiple peptic ulcer was used by German surgeons as their justification for their frequent practice of primary gastrectomy for perforated ulcer. He cites various authors as reporting multiple peptic ulcers in a high percentage of cases varying from 20 to 50 per cent. Among them were Schulein<sup>43</sup> who reported the incidence in 20 per cent, Petren<sup>43</sup> in 27 per cent, and Speck<sup>44</sup> in 50 per cent.

More recently, Guszi<sup>45</sup> has reported 7 cases of multiple ulcer (6.2 per cent) among 113 cases of perforated gastric and duodenal ulcers. He quotes various authors as reporting a much higher incidence. Zuckschwerdt and Eck<sup>46</sup> found in their autopsy material multiple ulcers in 29 per cent of the peptic ulcer cases, and Brunner<sup>47</sup> in his, either multiple ulcers or scars in 43 per cent. Brütt<sup>48</sup> found in his autopsy material 10 cases (53 per cent) of multiple ulcer among 19 cases of duodenal perforation, while in his resection material, the incidence was 17 per cent in the cases of peptic ulcer without perforation, and 70 per cent in the cases of peptic ulcer with perforation. Koennecke<sup>49</sup> reported the incidence of multiple ulcer as 50 per cent in his duodenal ulcer cases.

Granting that the incidence of multiple peptic ulcer in this clinic and others appears very significant, indeed, the wisdom of simple suture of perforated peptic ulcers as a routine method of treatment might be questioned. To be sure, the reported mortality statistics<sup>50</sup> for the other types of operation are often better, and those for primary gastric resection are even best. However, mortality statistics can be very misleading, and one can find almost any mortality rate desired for any given type of operation, depending almost entirely upon the lapse of time between perforation and operation, as is well known.

The late results for the other types over simple suture are reported as better, and again, as one would expect, those for primary gastric resection even best. However, even in view of the various considerations for and against the different types of operation,<sup>16, 50</sup> the primary consideration is still the survival of the patient. For this, one can hardly deny that simple suture is the easiest, quickest, and safest, and affords the patient the best possible chance of immediate recovery at any stage following perforation. To do anything further in the way of a curative procedure in the presence of an acute perforation merely subjects unnecessarily an estimated 50 per cent of patients to additional risk.

The most important consideration, however, as a result of this study, is the fact that these patients should be carefully followed at frequent intervals over a long period of time, possibly five years, in view of the large percentage who do not remain well. In the event of subsequent complete pyloric obstruction without the additional presence of an ulcer,

gastroenterostomy is known to be highly successful. And in the event of a persistence or recurrence of symptoms, in view of the large percentage of patients with multiple ulcer, secondary gastric resection is to be recommended.

#### SUMMARY

1. The late results in 18 cases of acute perforated peptic ulcer treated by simple suture are reported. Six patients (or 33 per cent) remained well, and 12 patients (67 per cent) did not remain well.
2. Six of the 18 patients were subjected to secondary operation, 3 of these being for a subsequent second perforation.
3. The late result in relation to age, duration of symptoms, diet and other factors, was studied without significant findings.
4. The late results reported in the literature for treatment by simple suture, suture plus gastroenterostomy, excision plus pyloroplasty, and primary gastric resection are reviewed.
5. In this clinic, the incidence of multiple peptic ulcers and/or scars in the surgical pathologic material was found to be 27 per cent (4 of 15 cases).
6. In this clinic, the incidence of multiple peptic ulcers and/or scars in the autopsy material was found to be 36 per cent (16 of 44 cases).
7. It is felt that this high incidence of multiple peptic ulcer is largely responsible for the poor late results obtained in the treatment of acute perforated peptic ulcer by simple suture.

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## THE SURGICAL MANAGEMENT OF POSTRADIATION SCARS AND ULCERS

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THE surgical management of the lesions caused by the tissue-destructive rays of both x-ray and radium presents problems which call for a knowledge of and the application of practically all of the principles of plastic surgery. The earliest report of a case of dermatitis due to x-rays is that of Marcuse, published in 1896. Marcuse<sup>1</sup> also reported a case of malignancy in an area of x-ray dermatitis. Since that time there have been a great number of similar reports. Their appearance in the literature suggests not only that these postradiation lesions probably are increasing in frequency, but that the medical profession is more alert to the value of and also to the dangers of radiation therapy. Undoubtedly, radiologists have given increasingly strict attention to the prevention of the development of these unfortunate complications. This is attested to by the repeated admonitions of competent radiologists with regard to the protection of patient and operator at the time of administration of the rays and also by the improvements in equipment and in the methods of treatment which have steadily expanded the field of usefulness of radiation therapy. It is a commentary on these improvements that clinical reports which appeared in the literature in the second and third decades of this century told of a higher percentage of x-ray ulcers occurring in physicians giving the therapy than in patients so treated. Later reports reversed this proportion. Presumably this is due to a recently born intensity of purpose on the part of radiologists in the therapy of malignant lesions. Such an unfortunate aftereffect as the postradiation ulcer may be condoned if produced in the treatment of inoperable malignancy. However, in the treatment of benign lesions or malignant ones within the scope of surgery, it is difficult to acknowledge the value of a method of therapy which carries with it danger of serious complication.

The burden of management of these postradiation ulcers has fallen upon the surgeons. It is planned to list in this presentation the methods of conservative treatment and also to outline the surgical methods which may be applied to the various types of postradiation scars and ulcers. Case reports giving experiences with the surgical removal of postradiation scars and ulcers will be presented.

<sup>1</sup>Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

Clinical examination of the scars produced by x-radiation shows them to be characteristically of firm consistency, depressed below the adjacent surface, and demarcated abruptly from it or blending gradually into the areas of normal adjacent skin. Often there is subcutaneous atrophy, evidencing the penetration of the destructive ray with its resultant subcutaneous fibrosis. The scarred area may be uniformly white in color or it may show areas of pallor alternating with areas of brown coloration. There may be clusters of telangiectases, visible as reddened wormlike areas in the background of white scar tissue. Often these scars are adherent to underlying structures such as fascia, muscle and bone. Their surfaces may be smooth or hyperkeratotic. In the latter type epithelial degeneration into carcinomatous malignancy is suggested. These differ, then, from the hypertrophic scars of thermal burns and they do not have the tendency to local recurrence exhibited by the true keloid.

Observation of the ulcers caused by radiation shows them to be punched-out ulcers, the lateral walls of which are made up of thickened, ischemic fibrous tissue. The most central portion of the scarred area, the point of maximal ischemia, is the area in which ulceration is most likely to occur. The floor of the ulcer may be covered with a thick, sticky, elastic, grayish yellow exudate which is easily removed to expose pale, firm granulation tissue or smooth, dense fibrotic tissue. These ulcers usually are very sensitive and may be excruciatingly painful. On microscopy the corium and subcutaneous tissue are seen to be replaced by dense fibrous tissue often invading the subadjacent fascia and muscle. There is thickening of the walls of the blood vessels with endothelial obliteration. Necrosis of underlying bone is commonly observed. The epithelium shows a flattening of the rete cones and in those cases which have undergone malignant change there are whorl formations of epithelial cells characteristic of the squamous-cell carcinoma. Malignant epithelial tumors of the basal-cell type are also observed in these scars, and sarcomas developing in these lesions have been reported in numbers in the literature. It is difficult to explain the development of malignancy in these ulcers. Repeated trauma to these areas undoubtedly is a factor. The fact that many cases of malignancy have developed in areas of the skin originally treated for inflammatory lesions, such as psoriasis, eczema, and tuberculosis, suggests the possible role of cutaneous infection in the development of the malignancy. Deuticke<sup>2</sup> reported sixty-one cases of roentgen sarcoma following treatment of inflammatory lesions. Experimental work on rabbits reported by Burrows and associates<sup>3</sup> lends support to this idea. They stated that 66 per cent of rabbits to which x-ray had been given after the experimental production of an inflammation of the skin developed carcinoma.

Regarding the dermatological treatment of postradiation scars and ulcers, it may be said that a number of widely different methods have been acclaimed. Treatment with ultraviolet light,<sup>4</sup> Finsen-Reyn lamp,<sup>4</sup>

electrodesiccation,<sup>5</sup> radium, sacriification,<sup>5</sup> trichloroacetic acid cauterization,<sup>5</sup> Dodd's solution (containing phenol),<sup>5</sup> ointment containing pancreatic ferments,<sup>6</sup> and the application of fresh leaves of the plant *aloe vera*<sup>7</sup> have been recommended. The last mentioned has been endorsed by MacKee<sup>8</sup> for ulcers with the qualifying statement that the treatment is of no value in the attempted removal of telangiectases, scars, keratoses, or atrophy. It is generally agreed that the application to the skin of such chemicals as sulfur, scarlet R, mercury, pyrogallie acid, iodine, resorein, tar, salicylic acid, and cantharides may raise the sensitivity of the skin to the x-ray. It seems likely also that electrodesiccation, actinic ray and radium may act to accelerate further the destruction of tissue rather than to retard it. Essentially, then, the problem presents itself as one of wound healing to be accomplished in tissues known to be deprived of their normal capacity for growth and repair. The additional problem of reconstruction of the surface contour of the affected area demands that all of these lesions be treated by surgical methods.

The methods available in the surgical management of postradiation scars may be listed as follows:

1. Simple excision
2. Excision and primary suture by means of sliding flaps
3. Gradual partial excision
4. Excision and replacement by
  - a. Thick-split graft
  - b. Whole thickness graft
  - c. Pedunculated flap

In the management of the indolent ulcers resulting from radiation therapy the following methods may be utilized:

1. Simple excision
2. Excision and primary suture by means of sliding flaps
3. Excision and replacement by
  - a. Multiple small deep grafts after a period of antisepsis to allow granulation tissue to form
  - b. Thick-split grafts
  - c. Pedunculated flap
4. Amputation
5. Section of regional nerves
6. Periarterial sympathectomy

The type of pedunculated flap to be used depends upon the surface location of the lesion. Thus, gauntlet flaps have been used for the fingers, double pedicled flaps in the region of the anus, tubed pedicles for lesions of the torso, face, neck, and extremity. Amputation is seldom indicated except in those ulcers of the fingers in which the pain is unbearable, or which have become malignant. Periarterial sympathectomy

has been advocated for relief of pain and for its benefit in bringing about healing of the ulcer. Leriche and Fontaine<sup>9</sup> have reported complete cure by this method in 12 of 27 cases, relief from pain and improvement in 7 cases, and failure in 8 cases. Tempsky<sup>10</sup> reported 2 cases in which there was temporary relief from pain and partial healing of the ulcer following periarterial sympathectomy with later recurrence of the painful ulcer. Eddowes<sup>11</sup> in 1910 reported relief of pain and healing following section of regional nerves. Later surgical reports do not emphasize this method of treatment.

The following case reports give the details of surgical treatment in ten cases with which I have had experience at the New York Hospital. The problems presented by these cases comprise many of the problems of indolent wound healing and exhibit nearly all of the methods of surgical treatment.

The first case is one in which x-ray therapy was given for the treatment of an enlargement of the thyroid. The deforming scar later necessitated surgery. The scar was excised and the wound closed by means of sliding flaps. Undoubtedly, surgical treatment of the goiter would have been preferable to x-ray therapy in this case.

CASE 1.—(M. E., N. Y. H. Case 230039.) This is the report of a 33-year-old white woman who noticed a swelling in the left side of her neck for the first time in 1932. A physician told her that this was a goiter and advised x-ray therapy. There were no symptoms of hyperthyroidism. Following intensive therapy over a period of three months in 1933, the swelling completely disappeared. Accurate information concerning the total dosage of x-radiation is not available. Upon completion of the treatment, an ulceration of the skin appeared over the area treated. Dressings were necessary for three months. The resultant deformity was a cause of concern to the patient not only because of its unsightly appearance but also because of the symptom of itching.

Examination, six years after this treatment, showed an ivory white reetangular scar with numerous telangiectases on its surface. It occupied a rectangular area measuring 9.5 by 4 cm. in the left anterior cervical region. The thyroid gland was palpable, the left lobe being slightly larger and firmer than the right. The scar was movable on the underlying tissues but caused visible adherent depression on deglutition. At operation nine months ago the operator was prepared to do a whole-thickness graft, but found that because of the ease with which the flaps of skin and platysma muscle were mobilized in the neck, the wound could be closed by primary suture. Flaps from either side were brought toward the center, the final line of suture conforming to the outline of the letter H. Because the sheath of the platysma could be sutured firmly with buried sutures of fine silk, the tension on the line of suture was not great. Microscopic examination of the tissue removed at operation showed atrophy of the epidermis and replacement of the dermis with dense, avascular, connective tissue. Figs. 1, 2, and 3 show the preoperative appearance, technique of operation, and final result. Follow-up examination nine months after operation showed no recurrence of the condition.

The second case is one in which radium and x-ray therapy, given in treatment of a benign lesion (hemangioma), caused a deforming scar of

the cheek which necessitated three operative procedures to effect its removal by gradual partial excision. Most probably surgical excision of the primary lesion would have been preferable.

CASE 2.—(L. L., N. Y. H. Case 158604.) This is the case report of a 17-year old girl who was examined for the first time in this clinic in April, 1937. She complained of a rectangular white, depressed scar of the left malar region which resulted from treatment of an angioma during infancy. The mother has described this as a port-wine stain. When she was 15 months old, the region was treated with carbon-dioxide snow to the point of blistering, but without eradication of the lesion. At 18 months of age treatment was instituted with radium plaques and followed by x-ray therapy. In the years before she came to this clinic she consulted dermatologists on several occasions and had been discouraged repeatedly as to the benefit of any further treatment.



Fig. 1.

Fig. 2.

Fig. 1.—Case 1. Adherent scar of neck following x-ray therapy for disease of the thyroid gland. Note the central pallor and the telangiectases at the periphery.

Fig. 2.—Case 1. Appearance of the patient two months after excision of the post-radiation scar.

Examination showed a depressed, white, flat scar measuring 3 cm. across and 3.5 cm. from above downward. This was removed by gradual partial excision, three operations being performed in April, 1937, May, 1937, and August, 1938, respectively. All of these operations were done under local anesthesia without hospitalization. The prolonged interval between the second and third stages was occasioned by the fact that minor infection developed in the wound after the second stage. Following each procedure a crepe lisse<sup>12</sup> dressing was employed for six weeks. This consisted of ordinary indestructible chiffon impregnated with collodion and applied over the entire cheek. Such a dressing serves to immobilize the face so that not even facial expression causes movement of the tissues. This relieves the recent wound of undue tension during the early postoperative weeks when ordinary facial mo-

tions may cause undue widening of the scar. Microscopic examination of the tissue removed showed dense reaction of fibrous tissue in the corium and subcutaneous tissue and flattening out of the rete cones of the epidermis. Figs. 4, 5, and 6 show the preoperative appearance, the technique of operation, and the final result. Follow-up examination two and one-half years after the final operation showed no widening of the scar.

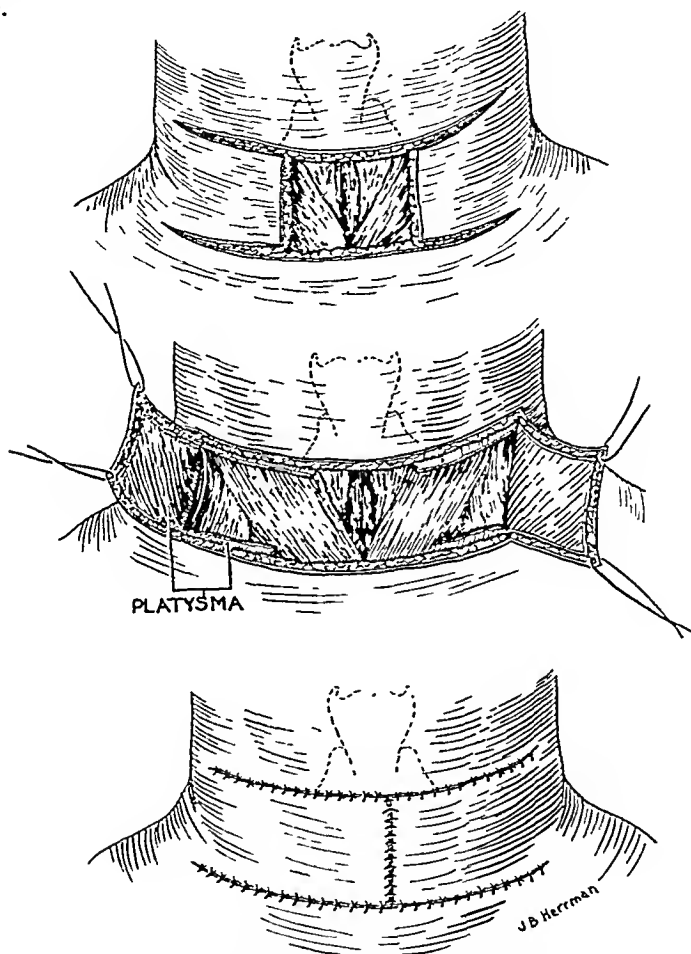


Fig 3.—Case 1. Technique of excision of scar and plastic closure of defect by means of sliding flaps and primary suture.

The next case is another instance in which x-ray and radium therapy produced a scar which itself constituted as much of a deformity as did the original lesion. In addition the lesion (pigmented mole) was not removed completely, and the treatment caused atrophy of the subcutaneous tissue. Since the patient was subjected to successful surgical excision and surfacing of the defect on the face with a whole-thickness graft, it seems likely that it would have been better to have employed this method of treatment instead of radiation many years earlier.



Fig. 4.

Fig. 5.

Fig. 4.—Case 2. Depressed scar of cheek following treatment of an angioma with carbon-dioxide snow, x-ray and radium therapy.

Fig. 5.—Case 2. Result following gradual partial excision of the scar (three-stage operative procedure).



Fig. 6.—Case 2. Diagrammatic sketch showing the steps in excision of a post-radiation scar of the cheek by the method of gradual partial excision. The outline of the extent of excision and suture employed in the first operation is shown in A and A'; for the second operation in B and B'; in the third operation in C and C'.



CASE 3.—(G. W., N. Y. H. Case 250979.) This is the case report of a young woman, 23 years of age, who was treated during infancy for a hairy mole on the right cheek. Acid cauterization was used. Because of the pain caused by this treatment, it was discontinued. At the age of 4 years the patient received prolonged treatments with both x-ray and radium. No accurate information is available as to the total amount of radiation given.

On examination a depressed scar measuring 6.5 by 3.5 cm. was seen over the right malar region. Subcutaneous atrophy was in evidence and the scar itself, while smooth, presented a rather severe deformity, since there were color variations within it from white to red to brown. The brown color apparently was due to residual pigmented nevus since it was limited to a smaller area within the scar, approximately 3 by 4 cm. in size. Evidently the therapy had failed to eradicate completely the hairy mole and also had produced deformity over an area greater than that of the original lesion. There was no regional adenopathy.



Fig. 7



Fig. 8.

Fig 7—Case 3 Depressed scar of cheek following treatment of a hairy mole by cauterization, x-ray, and radium. The darker central portion was brown in color due to incomplete removal of the mole.

Fig 8—Case 3 Appearance following excision of the pigmented scar and surface replacement by means of a free, whole-thickness graft taken from the abdomen. Photograph taken ten weeks after operation.

On Nov. 14, 1939, under local anesthesia, this scar was excised, care being taken not to damage the fibers of the facial nerve. A whole-thickness free graft of skin was cut from the right lower quadrant of the abdomen according to a tin foil pattern of the defect on the side of the face. The superficial abdominal defect was closed by excision of subcutaneous fat and undercutting of wound edges. The graft was sutured into place on the face with interrupted sutures of fine black silk. The long ends of these sutures were tied over a gauze pad for immobilization. The incisor teeth were wired together by Dr. Harold Genvert of this clinic. The head dressing, incorporating rubber sponge, was applied over the right cheek and the wound was not inspected until the sixth day after operation, at which time it was seen that the graft had taken in its entirety. The patient was discharged from the hospital on the twelfth day after operation. Microscopic examination of the specimen showed that the corium was replaced by dense fibrous tissue. The rete cones were flattened

out. There was hyperplasia of the nevus cells and beneath the epithelium there were groups of chromatophores containing brown pigment. The preoperative and post-operative photographs are shown in Figs. 7 and 8. Examination fifteen months after operation showed the graft to be smooth, pliable and a good match in color to that of the adjacent skin.

The fourth case is one in which the indication for deep x-ray therapy given in 1918 is not quite clear. Of interest is the fact that a severe skin reaction developed during the course of radiation and healed completely as treatment was continued only to give rise to ulceration eighteen years after the last treatment had been given.

CASE 4.—(M. S., N. Y. H. Case 268989.) This case is that of a 69-year-old American-born housewife who gave the history of having been treated intensively with low voltage x-ray to the lower abdomen twenty-two years earlier. This treatment was given to control hemorrhage following abdominal operation. The history is obscure as to the nature of the operative procedure. Apparently a panhysterectomy had been done, since, at the time of admission to the New York Hospital, examination revealed that none of the pelvic organs could be palpated. During the course of x-ray therapy a severe skin reaction developed over the lower abdominal wall. This healed spontaneously and the patient was free from symptoms until four



Fig. 9.—Case 4. Benign ulcer of the lower abdominal wall which developed in an area of radiodermatitis eighteen years after the last x-ray treatment had been given.

years before admission to this hospital. This was eighteen years after the last x-ray treatment had been given. At that time a thickening of the skin in the right lower quadrant of the abdomen was noticed. This developed into a hard cutaneous mass which crusted and ulcerated alternately. Six months before admission, eczema of the abdominal wall, limited to the two lower quadrants, developed. This responded to therapy with lotions, and on July 23, 1940, the patient was admitted to the New York Hospital for excision of the crusted, elevated lesion of the skin of the right lower abdominal quadrant. The appearance of the lesion at the time of admission to the hospital is shown in Fig. 9. On examination of the abdomen it was seen that there was excessive cornification of the skin of the lower abdominal wall. Just over McBurney's point there was an elevated, hard tumor of the skin 2 by 2 cm. in size. In its central portion there was a small ulcer. This lesion had the appearance of an epithelioma. At operation this area was widely excised through a transverse, elliptical incision. This incision was carried through the fibrotic subcutaneous tissue and the thickened anterior rectus fascia. The wound was closed with mattress sutures without drainage. Microscopic examination of the specimen showed a thickened, hyperkeratotic epidermis overlying a thick layer of scar tissue and fat in

which there were collections of chronic inflammatory cells. There was no evidence of malignancy. Superficial wound infection developed. This was readily controlled. The patient was discharged from the hospital on Aug. 14, 1940, twenty-one days after operation. Two weeks later the wound was entirely healed. On examination six months after operation it was determined that there had been no further symptoms. Photograph of the appearance of the lower abdomen on February 5, 1941, is shown in Fig. 10.

The fifth case is an example of the development of severe skin reaction with resultant chronic ulceration following intensive x-radiation for the treatment of glandular metastases from a malignant melanocpithelioma. It is this type of case in which the radiologist and surgeon justifiably may agree to carry the patient up to the limit of skin tolerance of the x-ray in the attempt to control a disease which is beyond the scope of surgery.



Fig. 10.—Case 4. Appearance of the lower abdomen six months after excision of the benign ulcer due to radiodermatitis.

CASE 5.—(M. S., N. Y. H. Case 261163.) This report is that of a 44-year-old American single, white female, who was examined for the first time on March 14, 1940, because of the complaint of a swelling below the left clavicle. The history revealed that eleven years earlier the left ring finger had been amputated at another institution. Report from that hospital revealed that the lesion of the finger was diagnosed microscopically as a malignant melanocpithelioma. A lymph node was removed from the infraclavicular region. Microscopy showed this to be a metastasis. X-rays of the neck and chest revealed no sign of other metastases. Over a period of six weeks x-ray therapy was given through three portals as follows: left infraclavicular, 4,700 R.; left lateral neck, 4,700 R.; left infraclavicular (lateral), 2,000 R.

X ray therapy had to be discontinued because of a severe skin reaction over the left cervical and infraclavicular regions. There was a large raw surface covered with a yellow exudate. The infraclavicular swelling had disappeared. There was subsequent softening of tissue in the central part of this wound with the result that as epithelialization occurred over the major part of the wound, this central portion persisted as an ulcer. Dry sterile dressings were applied daily and excision of the ulcer was contemplated, but the patient entered the hospital in a comatose state eight months after the metastasis in the infraclavicular region had been revealed. The patient expired on Dec. 22, 1940. Death was due to hemorrhage into the cerebellum and pons. Microscopic examination of the ulcer of the chest wall showed dense fibrosis, avascular granulation tissue, and replacement of the subcutaneous tissue with fibroblasts. Photograph of the lesion is shown in Fig. 11.

Another case report is one in which the postradiation effect (ulceration of the abdominal wall) is justified in view of the fact that the therapy in this case has effected control of malignant disease.

CASE 6.—(C. S., N. Y. H. Case 78062.) This is the report of a 57-year-old German-born housewife who was given five series of x-ray treatments to her lower abdomen for squamous-cell carcinoma of the cervix in 1934 and 1935. The total amount of x-radiation given was 18,280 R. units; 3,600 mg. hours of radium were applied. The last treatment was given in 1935. The lesion of the cervix healed completely without extension. There had been no evidence of recurrence of carcinoma up to April 11, 1940, so that the patient has been listed as a five-year carcinoma cure.



Fig. 11.—Case 5. Ulcer of anterior chest wall following intensive x-radiation (11,400 R. over a period of six weeks) for metastatic melanoeplithoma.

In December, 1938, the patient was admitted to the hospital because of the late development of ulceration of the lower abdominal wall. This came on three years and three months after the last x-ray treatment was given.

Examination showed a brawny indurated area covering the lower abdomen, with scarring of the skin and numerous telangiectases. Two ulcers measuring 3 and 4 cm. in diameter were present within the scar. These presented an unhealthy gray granulation tissue, from the surface of which *Staphylococcus aureus* was cultured. In January, 1939, this patient was operated upon under general anesthesia. A large elliptical incision with its long axis transverse was made around the scar. Laterally, this incision extended to the iliac crests on both sides, superiorly to a point 3 cm. below the umbilicus, inferiorly to the symphysis pubis. The incision was carried down to the fascia of the external oblique on both sides. The tissue was almost completely avascular. The induration extended into the rectus muscle but not into the peritoneum. Microscopic examination of the tissue removed revealed atrophy of the epidermis, fibrosis of the dermis, and subcutaneous scar with acute inflammation. Thrombosis of large vessels in the subcutaneous tissue was noted. Without opening

the peritoneal cavity the operator was able to overlap the fascial structures from above downward with mattress sutures of chromic catgut, after the technique of the Mayo hernioplasty. Postoperatively, there was an elevation of temperature and liquefied fat discharged from the right side of the wound. Culture again showed *Staphylococcus aureus*. All sinuses were healed in March, 1939, two months after the operation. The patient was seen in March, 1940, fourteen months after the



Fig 12—Case 6 Lesion of lower abdominal wall with ulceration and extensive regional fibrosis. This followed intensive treatment with x-ray and radium for squamous-cell carcinoma of the cervix.



Fig 13—Case 6 Appearance of the abdomen seven months after excision of the ulcerated and infected area. This patient was examined five years after the last radiation treatment was given and fifteen months after surgical excision of the lesion of the lower abdominal wall. No recurrence of carcinoma could be demonstrated at that time and the wound of the abdominal wall remained healed.

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Fig. 11.—Case 5. Ulcer of anterior chest wall following intensive x-radiation (11,400 R. over a period of six weeks) for metastatic melanocpithelioma.

In December, 1938, the patient was admitted to the hospital because of the late development of ulceration of the lower abdominal wall. This came on three years and three months after the last x-ray treatment was given.

Examination showed a brawny indurated area covering the lower abdomen, with searring of the skin and numerous telangiectases. Two ulcers measuring 3 and 4 cm. in diameter were present within the scar. These presented an unhealthy gray granulation tissue, from the surface of which *Staphylococcus aureus* was cultured. In January, 1939, this patient was operated upon under general anesthesia. A large elliptical incision with its long axis transverse was made around the scar. Laterally, this incision extended to the iliac crests on both sides, superiorly to a point 2 cm. below the umbilicus, inferiorly to the symphysis pubis. The incision was carried down to the fascia of the external oblique on both sides. The tissue was almost completely avascular. The induration extended into the rectus muscle but not into the peritoneum. Microscopic examination of the tissue removed revealed atrophy of the epidermis, fibrosis of the derma, and subcutaneous scar with acute inflammation. Thrombosis of large vessels in the subcutaneous tissue was noted. Without opening

the peritoneal cavity the operator was able to overlap the fascial structures from above downward with mattress sutures of chromic catgut, after the technique of the Mayo hernioplasty. Postoperatively, there was an elevation of temperature and liquefied fat discharged from the right side of the wound. Culture again showed *Staphylococcus aureus*. All sinuses were healed in March, 1939, two months after the operation. The patient was seen in March, 1940, fourteen months after the

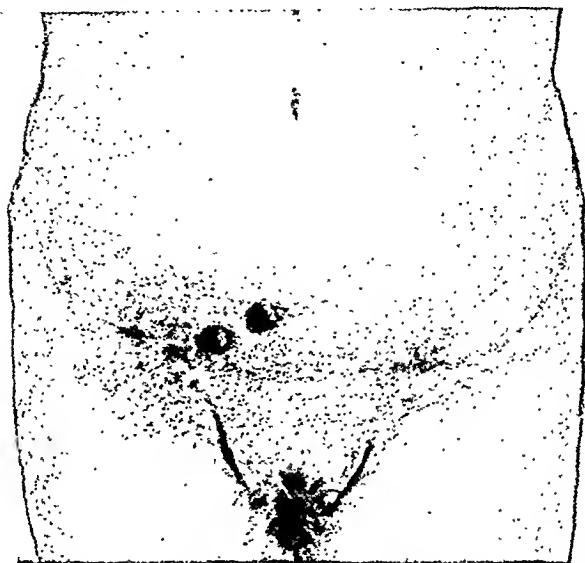


Fig. 12.—Case 6. Lesion of lower abdominal wall with ulceration and extensive regional fibrosis. This followed intensive treatment with x-ray and radium for squamous-cell carcinoma of the cervix.



Fig. 13.—Case 6. Appearance of the abdomen seven months after excision of the ulcerated and infected area. This patient was examined five years after the last radiation treatment was given and fifteen months after surgical excision of the lesion of the lower abdominal wall. No recurrence of carcinoma could be demonstrated at that time and the wound of the abdominal wall remained healed.

excision. There was no recurrence of carcinoma at that time and the wound remained healed. Figs. 12 and 13 show the appearance of the lower abdomen before and after operation.

The seventh case is an example of the development of malignant ulcer following x-ray treatment of a chronic inflammatory condition of the skin (psoriasis). The reports of Deuticke,<sup>2</sup> who listed 61 cases of malignancy following x-ray therapy for lupus, psoriasis, eczema, hypertrichiasis, and other inflammatory conditions, and of Witwer and

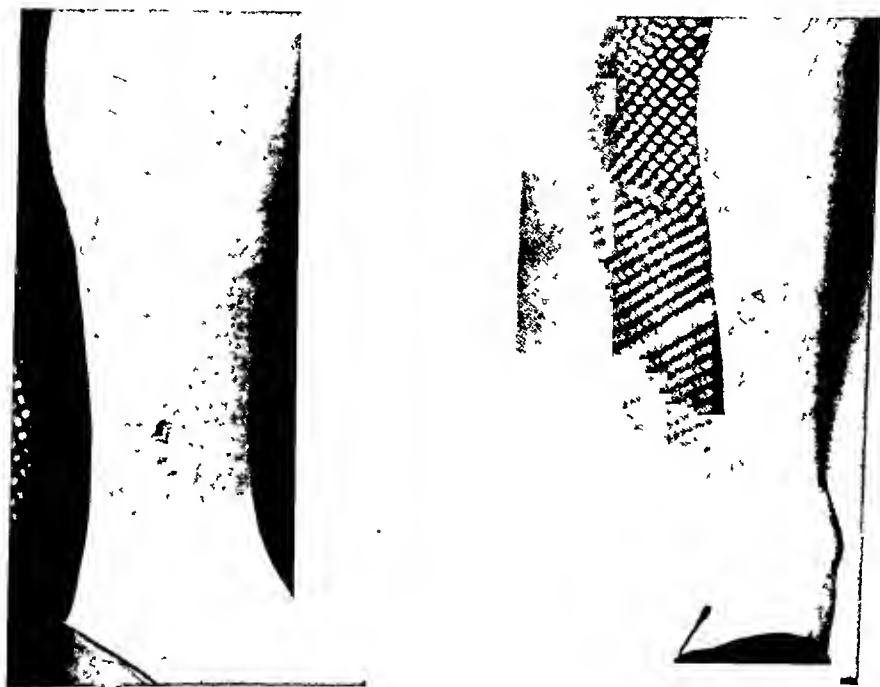


Fig. 14.—Case 7. X-ray treatment had been given to the area overlying the right lower fibula, as well as to other parts of the body, for psoriasis. In the sixteen months before this photograph was taken the ulcer was fibrotic, dry, hairless, and hyperkeratotic. The skin around the ulcer was open and ulcerated. The skin around the ulcer was psoriatic. Typical lesions of psoriasis show higher on the leg and over the posterior aspect of the lower leg. Microscopic examination of this lesion showed it to be a squamous-cell carcinoma.

Leucutia,<sup>13</sup> who recorded the development of malignancy in 20 cases after x-ray therapy for acne, keloid, hyperkeratosis, psoriasis, ringworm, sycosis barbae, etc., indicate that the sequence of events which occurred in this sixth case is well known. Unless x-ray therapy affords good probability of cure, it is not justified in the treatment of these chronic inflammatory diseases of the skin.

CASE 7.—(C. W., N. Y. H. Case 286661.) This case report is that of a 36 year-old American-born stock broker who had suffered from psoriasis with lesions over his back, elbows, and legs for fourteen years. In June, 1915, x ray treatments were started. These were given once a week for three weeks; similar treatments were given every two months over a period of eighteen months. In December, 1936, the



last x-ray treatment was given. In September, 1939, the patient injured the outer aspect of the lower third of the right leg. An ulcer developed. He applied various ointments to the ulcerated area without success. The ulceration increased in size and became painful. Another smaller ulcer developed below it. The appearance at the time of admission to the New York Hospital in January, 1941, is shown in Fig. 14. The larger ulcer measured 1.5 cm. in diameter. It was in the central portion of an area of dry and thickened skin which covered the outer aspect of the lower one-third of the leg. Numerous telangiectases were in evidence in this area and surface scaliness was excessive. A lesion, typical of psoriasis, showed somewhat higher on the outer aspect of the same leg. The floor of the ulcer was dusky purple in color. Superficial granulations bled easily. The ulcer was very sensitive. There was inguinal adenopathy on both the right and the left sides. None of the other psoriasiform lesions which had been treated showed any evidence of scar or ulcer. At operation the lesion was removed by wide elliptical excision extending down to the fascia and to the periosteum of the fibula. Microscopy showed that this was an epidermoid carcinoma. Biopsy of an inguinal gland showed no regional metastasis. The wound was dakinized and small deep grafts were applied after a period of seven days despite the fact that the granulation tissue never did appear healthy. About one-half of these grafts lived. Subsequently the wound was grafted six times over a period of three months before epithelization was complete. The wound has been healed for four months without recurrence of tumor or ulcer.

The eighth case, like Case 6, is one in which intensive radiation, purposely given, resulted in an apparent arrest of the malignant growth (adenocarcinoma of the ovary, inoperable) but with the late development of ulceration of the entire abdominal wall. Surgical removal of the affected area in this case was more difficult than in Case 6 since the entire thickness of the abdominal wall was involved. This patient, who has gone five years now without sign of recurrence of carcinoma represents, as does the patient in Case 6, an excellent result of x-ray therapy despite the difficult problem presented in the surgical cure of the post-radiation ulcer.

CASE 8.—(E. H., N. Y. H. Case 44089.) This case report is that of a 47-year-old unmarried female clerk who was given a total of 17,000 R. of x-ray radiation in six series of treatments, from 1933 to 1935, for inoperable adenocarcinoma of the right ovary. Two years afterward telangiectases appeared over the lower abdominal wall, followed by breaking down of the skin and development of ulceration. Conservative measures were carried out for an eighteen-month period, during which time the epithelium occasionally covered the ulcer only to be followed by recurrent ulceration.

Examination in 1935 showed a deep craterlike ulcer, 13 by 5 cm. in size, over the lower quadrants of the abdomen. This ulcer was floored by pale, gray granulation tissue, hard and fibrotic. For 5 cm. in all directions the tissue adjacent to the ulcer was indurated, thickened, and searred. On Aug. 2, 1939, this ulcer was excised through a transversely placed elliptical incision. The tissues were isehemic and fibrotic. The floor of the ulcer proved to be only 4 mm. thick, and in the process of excising it the peritoneal cavity was entered. The intestines were adherent to the underside of the abdominal wall. Attempts to close the fibrotic fascia and peritoneum were unsuccessful, and in order to close the defect in the abdominal wall, it was necessary to resort to the use of a rectangular free graft of fascia lata taken from the right thigh. When the peritoneal cavity had been closed in this fashion,

a flap of skin and subcutaneous fat was dissected up from the superior portion of the wound to a point well above the umbilicus. Because of the extensive induration in the femoral and perineal regions, it was not possible to mobilize a flap in the lower part of the wound. By flexing the thighs on the abdomen, that is, putting the patient in a jackknife position, it was possible to close the margins of the wound with deep on-end mattress sutures of dermal gut. This wound subsequently broke down with recurrence of the ulcer. The fascial graft did not slough and the floor of the ulcer presented pale granulation tissue. Dakinization was instituted and a thoracicopigastic tubed flap<sup>14</sup> was constructed at operation on Oct. 6, 1939.



Fig. 15.—Case 8. Photograph showing the painful, deep ulceration of the lower abdominal wall which followed intensive deep radiation given in treatment of inoperable adenocarcinoma of the right ovary. The ulceration extended down into the rectus muscles. There was much brawny edema of the pubic and vulvar tissues. Over these areas the skin was shiny, thickened, and showed alternate areas of pallor due to fibrosis and redness as a result of abundant telangiectases. The floor of the ulcer was pale gray in color. The margins of the ulcer undermined the overlying skin and subcutaneous tissue on all sides. Photograph taken July 31, 1939, four years after the last x-ray treatment had been given and two years after the first sign of ulceration was noticed.

On Nov. 22, 1939, this tube was detached at its upper portion and sutured into the lateral margin of the ulcerated area. Culture from this wound has shown *Streptococcus hemolyticus*, nonhemolytic streptococcus and beta-hemolytic streptococcus. On Dec. 27, 1939, scarred tissue was excised from the midportion of the ulcerated area and a larger section of the tubed pedicle was opened out and sutured into the wound. On Jan. 31, 1940, the remaining ulcerated area over the right lower quadrant of the abdomen was excised and the unused portion of the tube was sutured into this area. The patient was cared for in the dispensary until all sinuses had healed. On May 2, 1940, the tubed pedicle was detached from its point of origin near the iliac spine. Careful microscopic examination of the tissue removed

at operation failed to show evidence of malignant degeneration. Skin, subcutaneous tissue, and rectus muscle were replaced by dense fibrous tissue. There were perivascular collections of lymphocytes and the large number of plasma cells seen in the tissues was striking. The ulcerated area showed necrosis of tissue with polymorphonuclear leucocytes in its upper areas and lymphocytes and plasma cells in



Fig. 16.—Case 3. Photograph taken Nov. 1, 1939, showing the thoracicoepigastric tubed pedicle which was constructed at operation in preparation for surfacing the defect after excision of the ulcer. Tube measured 31 cm. in length. Previous attempt at excision of the ulceration with primary closure had met with failure.

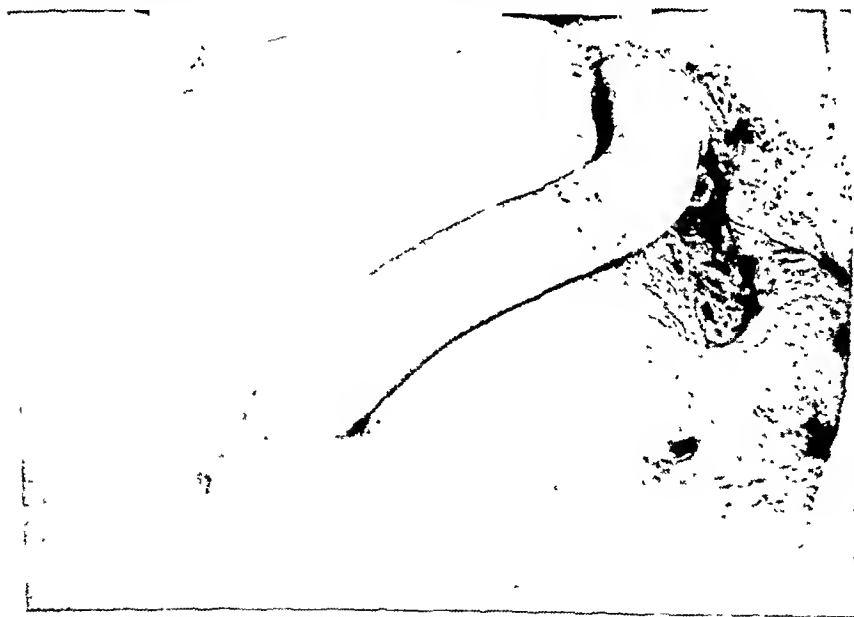


Fig. 17.—Case 3. Photograph taken Dec. 26, 1939, one month after detachment of the upper end of the thoracicoepigastric tubed pedicle and its suture into the left lower quadrant of the abdomen, lateral to the area of ulceration and fibrosis. This view is taken from the right side of the abdomen. After the construction of the tube an interval of forty-seven days elapsed before the upper end was detached and sutured as shown in this photograph.

the fibrous tissue beneath. The accompanying fat showed lymphocytic and plasma-cell infiltration. The microscopic diagnosis was postradiation atrophy of skin and subcutaneous tissues with chronic inflammation and ulceration. The patient has had no further complaints. She was examined in January, 1941, eight months after the

last operation. At that time there was no symptom or sign suggestive of recurrence of the malignancy of the ovary for which this patient was originally subjected to x-ray treatment. Photographs showing the appearance of the ulcerations and the successive stages are shown in Figs. 15, 16, 17, 18, and 19.

The ninth case is an example of the development of carcinomatous ulcer of the finger occurring in a physician who had been exposed to both x-rays and radium over a period of twelve years. The reports of Davis,<sup>15</sup> of Beclere,<sup>16</sup> and of Blair, Brown, and Hamm<sup>17</sup> tell of many other cases in which the physician was the unfortunate victim of the therapeutic measure which he employed. Witwer and Lencutia (1940)<sup>13</sup> reported that of 28 cases of malignancy in x-ray ulcers, 8 occurred on the hands of physicians, surgeons, or dentists. Fortunately, knowledge of the prevention of this development is now in the hands of all who work with x-rays and radium.

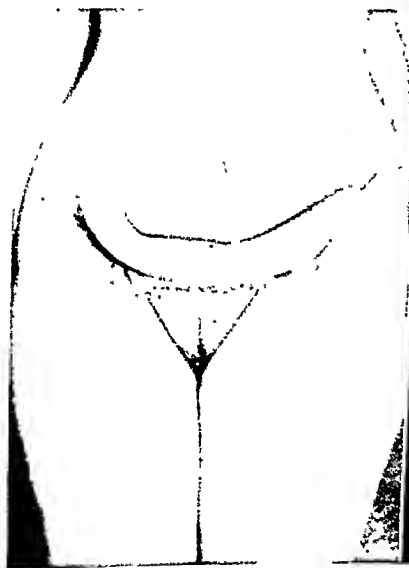


Fig. 18.



Fig. 19.

Fig. 18.—Case 8. Photograph taken Feb. 15, 1940, two weeks after excision of the midportion of the ulcer and suture of the tubed flap into the midabdominal and right lower abdominal wall. The flap is still attached by its pedicle to the point of origin just medial to the anterior iliac spine.

Fig. 19.—Case 8. Photograph taken May 23, 1940, three weeks after the detachment of the lower end of the thoracicoepigastric tubed pedicle. This was the final operation. The patient has been followed for eight months following this procedure. There has been no recurrence of ulceration or sinus and there has been no sign of recurrence of the carcinoma of the ovary for which the patient was treated originally.

CASE 9.—(N. Y. H. Case 276982.) This case report is that of a 53-year-old surgeon who for twelve years had been exposed to x-rays in fluoroscopic work and to radium in direct application in the practice of his profession. One year before admission to the hospital (Sept. 11, 1940), he noticed crusting of the skin over the distal phalanx of the left middle finger. Several months later the area ulcerated. Subsequently, this area healed only to ulcerate again following the mildest trauma. Four months before admission a small nodule appeared over the middle third of the

same finger on its dorsal radial aspect. This nodule grew slowly in size and two months after its appearance it developed into an ulcer. The lesion was exquisitely tender and gave rise to lancinating pains shooting up the forearm to the elbow.

On examination the lesion presented itself as a punched-out ulcer 3 mm. in diameter with elevated edges through a diameter of 1.2 cm. There was no epitrochlear or axillary adenopathy. Over the dorsal surfaces of the other fingers and thumbs of both hands there were several nontender, firm nodules 2 by 4 mm. in diameter. The finger was amputated at the metacarpophalangeal joint. Microscopic examination of the specimen showed it to be a squamous-cell carcinoma which had not invaded the periosteum or the tendon sheaths. The epidermis was greatly thickened and extremely hyperkeratotic. Chronic inflammatory cells were scattered throughout the corium. The patient has remained well in the five months since amputation of the finger. Artist's sketch of the appearance of the lesion is shown in Fig. 20.

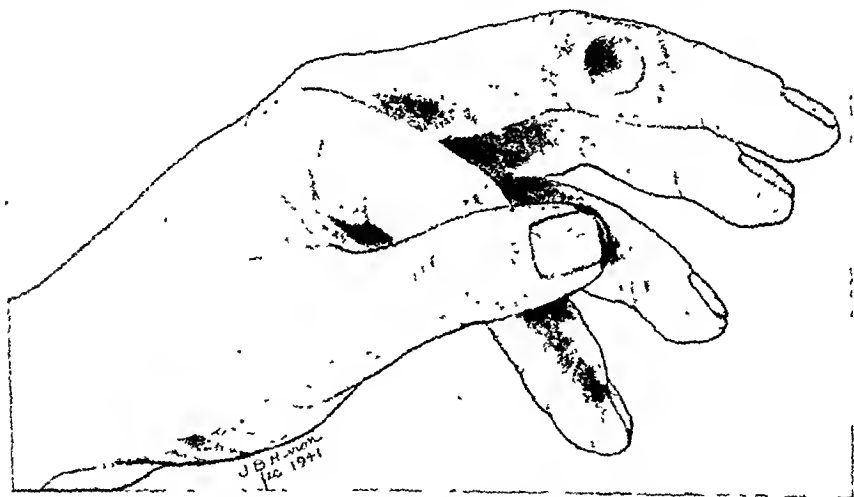


Fig. 20—Case 9. Painful ulcer of middle finger occurring in a physician who for twelve years had been exposed to x-rays and radium. The lesion proved to be a squamous-cell carcinoma.

The story in the tenth case is regrettable in that malignancy of the skin of the face developed after x-ray treatment for acne. Referring again to the report of Witwer and Lenentia,<sup>13</sup> 3 of 28 cases of roentgen malignancy followed treatment for acne. It seems to me that x-ray therapy is not justified in the treatment of acne not only because of the possibility of the late development of carcinoma, but also because the treatment causes such diffuse scarring of the skin and subcutaneous tissues. Niles<sup>14</sup> has reported clinical experiments in which patients were subjected to x-ray treatment of only one side of the face. His conclusion was that x-ray does not cause fibrosis of the skin of the face when given for acne. However, it is my impression from experience with a great number of patients who sought relief from the deformity presented by scarred skin of the face after x-ray treatment for acne

that the technique of administration of the ray and the response on the part of the tissue is not sufficiently standardized to bear out Niles' conclusions.

CASE 10.—(R. M., N. Y. H. Case 272543.) This case report is that of a 26-year-old American-born girl who had suffered from severe facial acne in the adolescent years. At 13 years of age she was given about twenty x-ray treatments over the nose, cheeks, and chin. These treatments left her with an x-ray burn of the lower face. Later, electrolysis was done by a physician for the removal of hair from the lower face. The patient complained of the tightness, pallor, and shiny appearance of the skin over her nose, cheeks, and chin from the date of completion of the x-ray treatments, but it was not until July, 1939, twelve years after the last x-ray treatment was given, that she noticed a small dark spot on the chin. She traumatized this by squeezing it and subsequently noticed the appearance of many other small grayish black spots in the skin of the chin.



Fig. 21.



Fig. 22.

Fig. 21.—Case 10. Basal-cell carcinoma of the chin occurring twelve years after x-ray therapy for acne. Note the cluster of pigmented areas over the left lower chin. These areas varied from 1 to 2 mm. in size and were gray-black in color.

Fig. 22.—Case 10. Result after excision of pigmented areas from right side of chin with primary closure and excision with whole-thickness graft to left side of chin.

On examination the appearance of the patient was as shown in Fig. 21. The skin of the entire face was drawn, thin, and shiny. Over the nose, cheeks, and chin, areas showing loss of normal pigment alternated with areas in which telangiectases were prominent. Over the left side of the chin, extending from the lip obliquely downward and outward, there were twenty minute areas of discoloration. These varied from 1 to 2 mm. in diameter and appeared to be due to grayish black deposit in the corium. Another smaller area under the lower lip on the right showed the same pinpoint, gray-black discolorations. These were believed, at first, to be evidence of traumatic tattoo, possibly due to the electrolysis. Preliminary biopsy on July 17, 1940, showed that this was not so. Microscopic examination of the tissue removed showed scattered areas of metaplastic epithelial cells in the subcutaneous tissue. The microscopic diagnosis was hair matrix carcinoma of the chin. On July 26, 1940,

radical excision of the involved areas was carried out. Elliptical excision on the right side of the chin allowed for primary closure. On the left side of the chin it was necessary to insert a whole-thickness free graft of skin 3.5 by 2 cm. in size. This was taken from the left postauricular area. Postoperative immobilization of the area was accomplished by wiring of the teeth and by a pressure dressing using sponge rubber. There was tremendous edema of the lips in the early postoperative period. This subsided and the graft was a complete success. At no time was there any demonstrable adenopathy in the cervical region. This patient has been followed for twelve months. There has been no evidence of recurrence of the carcinoma. The postoperative appearance is shown in Fig. 22.

#### DISCUSSION

The cases recorded in this report serve to emphasize the fact that, due to the present widespread application of x-rays and radium, the number of severe postradiation burns, scars, ulcers, and malignant tumors is increasing. These constitute a danger which should not be minimized. Often these aftereffects result in amputation, in complete disability, occasionally in death. It is my firm conviction that x-ray or radium is not justifiable for the treatment of benign lesions when these are of a type and location that make them surgically accessible. The advancement of the principles of plastic surgery and the utilization of these principles in the management of both benign and malignant tumors of the surface of the body will serve to assign a greater percentage of tumors of the skin to the field of surgery. The increase in the number of reported cases in which malignancy has followed the x-ray or radium treatment of inflammatory conditions of the skin is a regrettable circumstance which should be recognized by the profession. It is not my contention that, in the light of present knowledge, all malignant tumors should be treated by surgical excision. A combination of surgery and radiation is certainly desirable. However, radiation in such cases should be given only by competent radiologists who have a full appreciation of the danger of the elements employed.

#### SUMMARY AND CONCLUSION

Ten case reports are given in which deforming scars, indolent ulcers, or malignancy developed following x-ray or radium therapy. In six of these this therapy was employed for the treatment of benign lesions; of these, two developed x-ray carcinoma. Another case was that of a physician who developed carcinoma of a finger due to excessive exposure to the rays. In three cases, the postradiation ulcers developed after intensive treatment of inoperable malignancy.

Methods of surgical management of these deformities are listed, and examples of many of them are given.

It is concluded that conservative measures are of little value in the eradication of the aftereffects of x-ray and radium and that these lesions

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# SHOULD THE PLEURAL SPACE BE REDUCED IN SIZE IN THE RESECTION OF LUNG TISSUE?

## AN EXPERIMENTAL STUDY\*

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*(From the Department of Surgery of the University of Chicago)*

**I**INTRATHORACIC operations have enjoyed a high degree of success within recent years. At the present time resection of lung tissue for inflammatory and neoplastic lesions is a commonplace procedure. This marked advance has been due to several factors; namely, improvement in diagnostic methods, better preoperative preparation of the patient, more attention given to postoperative management, and improvement in operative procedures. Many unsolved problems remain in this field of thoracic surgery and in spite of the advancement there is much room for improvement in the present mortality and morbidity.

Clinically, the advisability of obliteration of the pleural space in resection of lung tissue in bronchiectasis and other destructive disease of the chest has long been a question of importance, particularly from the standpoint of the immediate postoperative convalescence and the late effects on the remaining lung tissue.

Many believe it advantageous to prevent overdistention and subsequent fragmentation of the parenchyma by reduction of the pleural space at the time of resection. Further, it is a question as to whether thoracoplasty should accompany or follow total pneumonectomy (Graham,<sup>1</sup> Reinhoff<sup>2</sup>). Such questions arise in the surgical treatment of bronchiectasis, tumors, and other conditions, where a large portion of the total lung is removed. Wound healing, obliteration of the pleural space, residual pneumothorax, cardiorespiratory effort, vital capacity, and the future comfortable existence of the patient may be markedly affected by these factors.

In recent work in this laboratory it was shown that the lung capacity in dogs could be reduced to 15 per cent of its total.<sup>3</sup> This experimental reduction was accomplished over a period of nineteen months by bronchial stenosis and by resection with subsequent stenosis. It was found that the procedure was best tolerated where a four- to six-week interval elapsed between stages of reduction. As a result of the overdistention of the remaining pulmonary tissue marked stretching and fragmentation of the alveolar walls occurred and persisted. In view of

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must be treated by surgery. Prevention of the occurrence of these complications of radiation therapy is a goal toward which the medical profession must strive.

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The muscle-splitting incision proved superior in our hands, the closure being more satisfactory and healing taking place with less sinus formation.

The surgical pneumothorax was partially or completely eliminated by use of a pneumothorax machine immediately upon discontinuation of the anesthesia.

The dogs were observed routinely for several hours after operation to note immediate changes. They were then returned to their quarters, no further special care being given. They were observed frequently thereafter for evidence of dyspnea, loss of weight, or any other change.

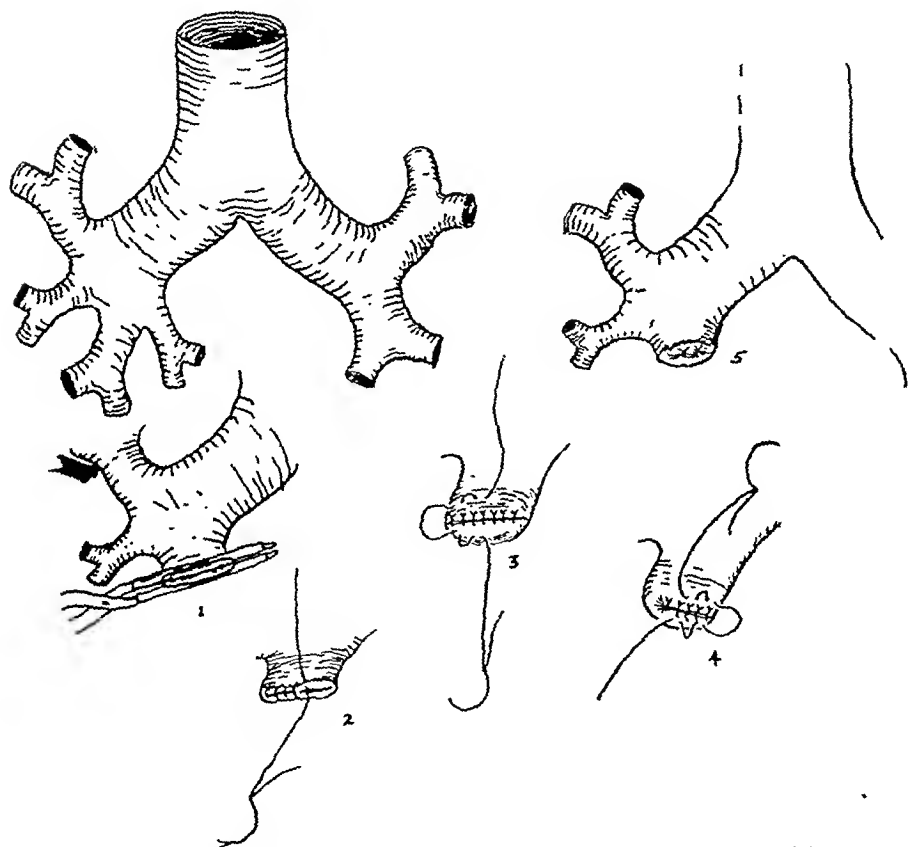


Fig. 1.—Diagrammatic illustration showing technique of closure of bronchial stump.

*Bronchial Stenosis.*—The dogs were given morphine and atropine before bronchoscopy. Cauterization with a 35 per cent solution of  $\text{AgNO}_3$  was then done in the manner described by Adams.<sup>2</sup> The bronchus usually closed after one or two applications. The dogs were bronchoscoped routinely at two-week intervals to check closure of the bronchus.

*Postoperative Course.*—Fluoroscopic and roentgenologic examinations with and without iodized oil were carried out at intervals to study the intrathoracic alterations. Electrocardiograms were also made.

the controversy over the clinical problem it was thought worth while to test the effect of partial obliteration of the residual pleural space on the ultimate physiologic and pathologic alteration of the remaining lung. This obliteration was accomplished by bilateral permanent paralysis, bilateral temporary paralysis, and unilateral permanent and temporary paralysis of the diaphragm. Thoracoplasty in dogs with its difficulty and associated high mortality has not as yet been studied very extensively.

#### EXPERIMENTAL WORK

Functioning lung tissue was reduced in a total of thirty-three dogs. Twenty-six dogs survived the first operation. These were subjected to a second operation and some of them to further reduction by bronchial stenosis. Various types of phrenic nerve paralysees were done at all operations. Healthy adult mongrel dogs of varying sizes and breeds were used in the work.

#### PROCEDURE

*Lobectomy.*—Morphine and atropine were used preoperatively. Intratracheal positive pressure ether anesthesia was used.<sup>4</sup> The technique varied as to the side of the first-stage operation. The approach was made by either dividing or splitting the muscles of the chest. Resections were done through the intercostal space or through a resected rib bed. The lobes were first mobilized by cutting the pulmonary ligament. The pulmonary artery was then isolated and sectioned after a triple ligation; two ligatures proximal and one distal. The pulmonary vein was then isolated and doubly ligated before section. The main bronchus was denuded and a soft right-angled clamp applied after which the lobe or lobes were removed by sharp dissection. The exposed mucosa was painted with a 10 per cent solution of  $\text{AgNO}_3$  and wiped with alcohol before closure was begun. Interrupted silk sutures were then placed in the bronchial stump. These sutures were numerous enough to occlude the bronchial arteries and to make the bronchus relatively airtight. The stump was then inverted by one or two semi-purse-string sutures of fine silk (Fig. 1). The phrenic nerve was either crushed or a 2 cm. section removed, permitting the diaphragm to rise. The water resistance to outflow from the ether mask was increased slightly (15 to 30 cm.  $\text{H}_2\text{O}$ ), to obliterate partially the pleural space before closure was effected. Care was taken never to exceed 20 to 30 mm. Hg wall pressure through the ether machine. Closure was carried out by an interrupted running No. 0 to 00 forty-day chromic catgut suture where the incision was through the resected rib bed; in the interspace incision, two double strands of No. 50 iron-dyed linen pericostal sutures were placed first, after which the interrupted running catgut suture was used. The muscle layers were closed with interrupted catgut sutures, subcutaneous tissue with interrupted fine silk, and the skin with interrupted black silk.

diaphragmatic paralysis accompanied the operations. About three months later the dog was able to tolerate a reduced pressure of 282 mm. Hg (25,000 feet) without loss of consciousness.

*Aug. 10, 1939.*—A right lower and accessory lobectomy was performed and the phrenic nerve sectioned. There was no dyspnea or other abnormal effect. The dog ate and was in good condition two days later.

*Oct. 14, 1939.*—Fluoroscopy revealed the chest cage aerated bilaterally. The right diaphragm showed no active motion. General condition was good.

*Oct. 30, 1939.*—A left lower lobectomy was performed through the sixth interspace and the phrenic nerve sectioned. Some difficulty was had uniting the anterior intercostal wound so that an astonishing degree of subcutaneous emphysema developed on the dog's left side. This extended even down the left leg. The dog was quite dyspneic at the end of operation but improved slightly after removal of 200 c.c. of air from the left chest. No air was found in the right chest. The condition was considered poor. There was marked improvement in twenty-four hours and no difficulty thereafter.

*Jan. 5, 1940.*—Fluoroscopy and bronchograms revealed the three remaining lobes filling the pleural space. Both diaphragms were paralyzed. (Fig. 3A.)

*Feb. 3, 1940.*—Bronchoscopy. A 35 per cent solution of  $\text{AgNO}_3$  was applied to the left upper lobe bronchus. The general condition was good.

*Feb. 17, 1940.*—Bronchoscopy. The left upper lobe bronchus was closed.

*March 3, 1940.*—Bronchoscopy. The right middle lobe bronchus was cauterized.

*March 19, 1940.*—Bronchoscopy. The right middle lobe bronchus was closed. Only the right upper lobe bronchus remained open.

*April 17, 1940.*—Fluoroscopy. The right chest was well aerated. The diaphragms were motionless, the left higher than right. The left upper thoracic region was dense.

*May 3, 1940.*—Bronchograms showed the right upper lobe aerated (Fig. 3B).

*June 5, 1940.*—The dog was placed in the evacuation chamber at 3:49 P.M. Some respiratory difficulty was exhibited at 395.4 mm. of Hg (17,000 feet). The dog was uneasy at a pressure of 364 mm. of Hg. (19,000 feet). There was slight dyspnea at 349.2 mm. of Hg (20,000 feet) and this was more marked at 282 mm. of Hg. (25,000 feet). The dog was unsteady, moved slowly about the cage. He fell down at 25,000 feet but was not unconscious. There was some cyanosis at 3:54 P.M. Pressure off at 3:55 P.M. The dog was out and walking about normally at 3:57 P.M.

This dog was not taken up faster or farther because he was not to be sacrificed.

*June 21, 1940.*—The dog was in good health. The respiratory effort suggested that the dog was dyspneic, but there was no cyanosis. He was unable to pant. (Dog 30 had same type of respiration.)

*February, 1941.*—This dog, No. 621, has remained in good health to date. At rest he still appears dyspneic due to the peculiar intercostal type of breathing. There is no cyanosis evident except on extreme exercise.

#### RESULTS OF EXPERIMENTS

The experimental work on the series of twenty-six dogs is presented in Table I. The dogs have been grouped according to the degree of obliteration of pleural space and to the amount of reduction in lung function beyond the two-stage operation. From a study of the chart it is apparent that Groups I, II, and VI represent primarily a study of the effect of varying degrees of reduction in pleural space; whereas, Groups III, IV, and V are a comparative study of various degrees of reduction in lung tissue or function.

*Test of Reserve.*—The dogs were exercised by running at intervals to observe signs of respiratory difficulty.

Further tests were carried out with an evacuation chamber into which the dogs were placed. The air pressure was then reduced, thus simulating high altitudes. Readings were made in thousands of feet. The pressure was decreased at the rate of 3,000 to 6,000 feet per minute until the dog lost consciousness. The chamber was then opened and the pressures equalized in one to two minutes.

Animals were sacrificed at various intervals by use of the electric current.<sup>6</sup> Gross alterations of thoracic contents were noted. Specimens of the lung were prepared by drying (air), by the Spaltcholtz method of clearing, by Wood's metal casts of the tracheobronchial tree, and by ordinary formalin fixation for histologic study.

PROTOCOL 1.—Dog 917. Healthy dog weighing 12.9 kg.

Reduction of lung function to 38.7 per cent of normal by bilateral operations which were performed seven weeks apart. Three months later this dog was able to tolerate reduction of atmospheric pressure to 502.6 mm. Hg which is equivalent to an altitude of 32,000 feet.<sup>8</sup>

*Jan. 12, 1940.*—A left lower lobectomy was performed through the sixth interspace and the phrenic nerve crushed. No dyspnea or other complication followed operation. Phrenic function returned in ten weeks as determined by fluoroscopy.

*March 7, 1940.*—A right lower and accessory lobectomy was performed through the seventh rib bed and the phrenic nerve crushed. After the operation there was slight dyspnea which had disappeared sixteen hours later.

The dog ate poorly for about one week, then gained rapidly. Fluoroscopy on April 17, 1940, showed the lungs aerated. There was no fluid or pneumothorax. The heart was in the midline. The left diaphragm was active; the right showed no active motion.

*May 10, 1940.*—Bronchography revealed the left upper and right upper and middle lobes aerated.

*June 4, 1940.*—Fluoroscopy demonstrated no fluid or pneumothorax and that considerable iodized oil remained in the lungs. The heart was in the midline. Both diaphragms were active.

*June 5, 1940.*—The dog was placed in the evacuation chamber at 11:35 A.M. The air pressure was reduced to 428.8 mm. Hg (15,000 feet altitude) in two minutes. There were no signs of distress and respiration was unchanged. At 411.8 mm. Hg pressure (16,000 feet) there was panting respiration. By 11:39 A.M. the pressure was reduced to 349.2 mm. Hg (20,000 feet). Respiration became slower and deeper at 307.4 mm. Hg (23,000 feet). The dog was in distress, trying to stand, fumbling about and salivating at 225.5 mm. Hg (30,000 feet). He fell over against the drum at 205.8 mm. Hg (32,000 feet) at 11:41 A.M. There was some dyspnea and cyanosis. The pressure was returned to normal at 11:42 A.M. The dog recovered and walked out of the chamber at 11:45 A.M.

*June 5, 1940.*—Sacrificed. The trachea clamped and chest opened. There was no hydro- or pneumothorax. The remaining lungs were adherent to the lines of incision and were moderately overdistended. The heart showed no abnormalities. See Fig. 6 for histology.

PROTOCOL 2.—Dog 621. A healthy white terrier of 10 kg.

Reduction of lung function to 15 per cent of normal by bilateral operations eleven weeks apart, plus additional collapse by bronchial stenosis. Bilateral permanent



months after the second-stage operation the left diaphragm had recovered its function. Five months after the last operation the left upper lobe was removed. The dog had no difficulty during the operation which was easily done. Afterwards, the respirations were deeper than normal. No cyanosis was present at any time. A temporary cardiac irregularity developed and an electrocardiogram was taken. This showed a tendency to premature auricular contractions and alternating extrasystoles. There was a tendency to slight left axis deviation. The dog did very well for one week and then suddenly began vomiting all food. He died on the twelfth postoperative day. At autopsy the lower third of the esophagus was markedly dilated. The left chest was free of fluid and air and the incision was well healed. The right upper lobe filled the upper portion of the left chest.

*Group III.*—Unilateral permanent paralysis of the diaphragm and reduction of lung function to 15 per cent of normal. The average time between operations was fifty-four days. Four dogs are shown. Dog 602 died after the second operation and at autopsy the right middle and upper lobes were atelectatic. Dog 612 was in a poor nutritional state and failed to survive the second operation. At autopsy a small empyema was found on the right side. Two dogs were reduced to one lobe.

*Group IV.*—Unilateral permanent and temporary paralysis of the diaphragm with reduction of lung function to 15 to 30 per cent of normal. The average time between operations was eighty-five days. Three dogs are shown and all had bronchial stenosis. Dog 636 was bronchoscoped on several occasions with cautery of the left upper lobe bronchus which failed to close. At autopsy this lobe was found to be consolidated. The lung function of Dog 687 was reduced to one lobe. He died following bronchoscopy about one week after the right middle lobe was closed. The dog had not seemed unusual and at autopsy there was no apparent cause of death. Dog 869 was reduced to two lobes but was unable to tolerate bronchoscopy after the preoperative sedation. Extreme cyanosis developed on several attempts.

*Group V.*—Bilateral permanent paralysis of the diaphragm and reduction of lung function to 15 per cent of normal. The average interval between operations was fifty-eight days. Four dogs are presented. There were two distemper deaths, one and two weeks after the final cauterization. One dog (No. 30) was sacrificed and one (No. 621) is living.

*Group VI.*—Bilateral temporary paralysis of the diaphragm and reduction of lung function to 30 per cent of normal. The time between operations was thirty-six days, the interval on the last two dogs being 22 days. Two dogs were sacrificed several months after the second stage operation, Dog 886 having had an additional thoracotomy for crushing the right phrenic nerve, which was not done at the second operation.

TABLE I

REDUCTION IN LUNG FUNCTION WITH OR WITHOUT OBLITERATION OF RESIDUAL PLEURAL SPACE IN 26 DOGS

GROUPS SHOWING TYPE OF PHRENIC PARALYSIS REDUCTION BY STENOSIS	DOGS IN GROUP	BILATERAL OPERATION	ADDITIONAL REDUCTION
I. Bilateral permanent paralysis*	7	7	0
II. Unilateral permanent paralysis and unilateral temporary paralysis	2	2	1 (operative)
III. Unilateral permanent paralysis and sublethal reduction	4	4	2
IV. Unilateral permanent, unilateral temporary paralysis and sublethal reduction	3	3	3
V. Bilateral permanent paralysis and sublethal reduction	4	4	4
VI. Bilateral temporary paralysis	6	6	0

\*Seven dogs not included in this group died after the first-stage operation from various causes (see text).

Table II shows in some detail the work on twenty-six individual dogs. The general grouping presented in Table I is followed. The reduction by operative stages and by bronchial stenosis is presented and the intervals between reduction are shown. These vary from three (Dog 939) to fourteen weeks (Dog 871). The causes of death or other end results are shown.

*Group I.*—Bilateral permanent paralysis of the diaphragm and reduction of lung function to 38.7 per cent of normal. Seven dogs are included in this group. The dogs had bilateral operations removing the left lower and right lower and accessory lobes. Phrenicectomy was performed at both operations. The average length of time between operations was sixty-nine days. Two operative deaths occurred from asphyxia, one due to a surgical pneumothorax and the other to the pre-existing fibrosis and atelectasis on the left upper lobe which was found at autopsy. Two deaths occurred twenty-four hours after operation due to distemper which had been present at the time of the second operation. Three dogs were sacrificed several months after the second operation. Their reaction to rarified atmosphere seemed normal.

*Group II.*—Unilateral permanent and temporary paralysis of the diaphragm and reduction of lung function to 38.7 per cent of normal. The average time between operations was sixty-nine days. It will be noted that dog 867 had a more extensive reduction at the first stage than usual, the right middle, lower, and accessory lobes being removed. Phrenicectomy was done. Five weeks later the left lower lobe was removed and the phrenic nerve crushed. This dog's postoperative course was not unusual aside from some coughing several weeks after operation. This we believed to be due to the loosening of bronchial sutures since bronchoscopy and x-ray examination revealed no other cause. The bronchial tree was well outlined by iodized oil (Fig. 2). About three

months after the second-stage operation the left diaphragm had recovered its function. Five months after the last operation the left upper lobe was removed. The dog had no difficulty during the operation which was easily done. Afterwards, the respirations were deeper than normal. No cyanosis was present at any time. A temporary cardiac irregularity developed and an electrocardiogram was taken. This showed a tendency to premature auricular contractions and alternating extrasystoles. There was a tendency to slight left axis deviation. The dog did very well for one week and then suddenly began vomiting all food. He died on the twelfth postoperative day. At autopsy the lower third of the esophagus was markedly dilated. The left chest was free of fluid and air and the incision was well healed. The right upper lobe filled the upper portion of the left chest.

*Group III.*—Unilateral permanent paralysis of the diaphragm and reduction of lung function to 15 per cent of normal. The average time between operations was fifty-four days. Four dogs are shown. Dog 602 died after the second operation and at autopsy the right middle and upper lobes were atelectatic. Dog 612 was in a poor nutritional state and failed to survive the second operation. At autopsy a small empyema was found on the right side. Two dogs were reduced to one lobe.

*Group IV.*—Unilateral permanent and temporary paralysis of the diaphragm with reduction of lung function to 15 to 30 per cent of normal. The average time between operations was eighty-five days. Three dogs are shown and all had bronchial stenosis. Dog 636 was bronchoscoped on several occasions with cautery of the left upper lobe bronchus which failed to close. At autopsy this lobe was found to be consolidated. The lung function of Dog 687 was reduced to one lobe. He died following bronchoscopy about one week after the right middle lobe was elosed. The dog had not seemed unusual and at autopsy there was no apparent cause of death. Dog 869 was reduced to two lobes but was unable to tolerate bronchoscopy after the preoperative sedation. Extreme cyanosis developed on several attempts.

*Group V.*—Bilateral permanent paralysis of the diaphragm and reduction of lung function to 15 per cent of normal. The average interval between operations was fifty-eight days. Four dogs are presented. There were two distemper deaths, one and two weeks after the final eauterization. One dog (No. 30) was sacrificed and one (No. 621) is living.

*Group VI.*—Bilateral temporary paralysis of the diaphragm and reduction of lung function to 30 per cent of normal. The time between operations was thirty-six days, the interval on the last two dogs being 22 days. Two dogs were sacrificed several months after the second stage operation, Dog 886 having had an additional thoracotomy for crushing the right phrenic nerve, which was not done at the second operation.

GROUPS	FIRST-STAGE OPERATION							SECOND ST.	
	DOG NO.	RESECTED		PIRENIC		RESULT		RESECTED	
		LOBES	DATE	CUT	CRUSH	WELL	DIED	LOBES	DATE
I. Bilateral, permanent paralysis	447	Left lower	4/ 6/39	+		+		Right lower and accessory	7/25/
	518	Left lower	5/ 3/39	+		+		Right lower and accessory	8/28/
	871	Right lower and accessory	12/18/39	+		+		Left lower	3/ 5/
	892	Right lower and accessory	12/27/39	+		+		Left lower	3/ 6/
	972	Right lower and accessory	2/ 9/40	+		+		Left lower	3/27/
	3	Right lower and accessory	2/16/40	+		+		Left lower	3/20/
	993	Right lower and accessory	3/ 2/40	+		+		Left lower	3/28/
II. Unilateral permanent and unilateral temporary paralysis	637	Right lower and accessory	9/29/39	+		+		Left lower	1/ 4/
	867	Right lower and accessory middle	12/13/39	+		+		Left lower	1/23/
III. Unilateral permanent paralysis and sublethal reduction	602	Right lower and accessory	7/31/39	+		+		Left lower	11/16/3
	612	Right lower and accessory	8/ 4/39	+		+	+	Left lower	11/ 1/3
	635	Right lower and accessory	8/31/39	+		+		Left lower	11/10/3
	695	Right lower and accessory	9/18/39	+		+		Left lower	11/14/3
IV. Unilateral permanent and unilateral temporary paralysis and sublethal reduction	636	Right lower and accessory	9/21/39	+		+		Left lower	1/ 8/4
	687	Right lower and accessory	9/27/39	+		+		Left lower	1/10/40
	869	Right lower and accessory	12/15/39	+		+		Left lower	1/24/40
V. Bilateral permanent paralysis and sublethal reduction	449	Left lower	4/26/39	+		+		Right lower and accessory	7/18/39
	30	Right lower and accessory	2/16/40	+		+		Left lower	3/20/40
	31	Right lower and accessory	2/19/40	+		+		Left lower	3/27/40
	621	Right lower and accessory	8/10/39	+		+		Left lower	10/30/39

FURTHER REDUCTION			REMARKS		
RESULT		STENOSIS			
USH	WELL	LOBES		DATE	
		+		Died when anesthesia was discontinued; operative	
		+		Died when anesthesia was discontinued; left upper lobe atelectatic; operative	
	+			6/5/40: evacuation chamber, 30,000 ft.; sacrificed	
	+			Died 3/7/40; right middle and part of left upper lobes consolidated; distemper	
	+			Died 3/28/40; right middle and part of left upper lobes consolidated; distemper	
	+			6/10/40: evacuation chamber, 25,000 ft.; sacrificed	
	+			6/5/40: evacuation chamber, 32,000 ft.; sacrificed	
+	+			6/5/40: evacuation chamber, 31,000 ft.; sacrificed	
+	+		Left upper lobectomy	6/19/40	Died 7/1/40; dilatation of esophagus with vomiting
		+			Died when anesthesia was discontinued; atelectasis of right middle and tension pneumothorax; operative
		+			Died as operation was being completed; emaciated and had small empyema on right; operative
	+		Left upper to 1 mm.	5/ 6/40	Killed in evacuation chamber at 26,500 ft.
			Right middle	5/31/40	6/5/40
	+		Left upper	2/ 3/40	6/7/40; evacuation chamber, 26,000 ft.; sacrificed
			Right middle	3/ 2/40	
+	+		Left upper failed to close		6/20/40: sacrificed
			Right middle	3/19/40	
+	+		Left upper	3/19/40	Died 3/25/40, no apparent cause; pneumothorax?
			Right middle	3/19/40	
+	+		Left upper	5/16/40	6/21/40: evacuation chamber, 24,500 ft.; sacrificed
	+		Left upper	10/7/39	Died 11/18/39, two weeks after last cauterization
			Right middle		Right upper and right middle consolidated; distemper
	+		Left upper	5/ 6/40	6/20/40: sacrificed
			Right middle	5/31/40	
	+		Left upper		Died 5/1/40, one week after last cauterization; right upper, right middle, and part of left upper consolidated; distemper
	-		Left upper	2/17/40	Evacuation chamber, 25,000 ft.; living
			Right middle	3/19/40	

TABLE

GROUPS	FIRST-STAGE OPERATION								SECOND-STAGE	
	DOG NO.	RESECTED		PHRENIC		RESULT			RESECTED	
		LOBES	DATE	CUT	CRUSH	WELL	DIED		LOBES	DATE
VI. Bilateral temporary paralysis	917	Left lower	1/12/40		+	+			Right lower and accessory	3/7/
	886	Left lower	1/22/40		+	+			Right lower and accessory	3/21/
	156	Right lower and accessory middle	5/9/40		+	+			Left lower	6/13/
	186	Right lower and accessory middle	5/10/40		+	+			Left lower	6/14/
	180	Right lower and accessory middle	5/22/40		+	+			Left lower	6/14/
	939	Right lower and accessory middle	5/23/40		+	+			Left lower	6/14/

The remaining four dogs were subjected to a trilobectomy at the first operation, and a second-stage left lower lobectomy about three weeks later. The left diaphragm of these dogs was not paralyzed. Their post-operative courses differed in no way from other dogs in the series. At a later date we plan to resect the left upper lobe and crush the phrenic nerve.

There were seven dogs which died after the first-stage operation. The causes of these deaths were as follows: two of wound infection and pneumothorax, two of distemper, one of erosion of an intercostal vessel causing fatal hemorrhage (this was at the site of the pericostal suture), one due to a gross bilateral empyema, and one operative death due to a needle puncture of the middle lobe. In the latter the pneumothorax could not be controlled and the dog died later during a reoperation in an attempted middle lobectomy.

It is obvious that these seven dogs represent the mortality for the entire series as regards survival of the first-stage operations; no other early deaths occurred.

Table III shows the immediate effects, late physiological and physical effects, and gross and microscopic findings after obliteration of the pleural space by phrenic nerve interruption. Diaphragmatic paralysis was permanent, temporary, and combined in character. As indicated, more marked gross overdistention of the remaining lung occurred in dogs with the temporary paralysis. On microscopic examination the most extreme degree of change was found in dogs with permanent paralysis. This change was in the terminal respiratory units.

Table IV shows the immediate and late effects of varying degrees of reduction in functioning lung. The causes of death are also indicated.

			FURTHER REDUCTION		REMARKS
C	RESULT		STENOSIS		
SH	WELL	DIED	LOBES	DATE	
F	+				6/5/40: evacuation chamber, 32,000 ft.; sacrificed
	+		Phrenic crushed	4/11/40	6/7/40: sacrificed
	+				Living
	+				Living
	+				Living
	+				Living

## IMMEDIATE EFFECTS

The immediate effects of reduction of lung function are presented in Tables III and IV. There was no cardiorespiratory embarrassment following bilateral resection of lung tissue or with additional reduction by bronchial stenosis, with the following exceptions: Dog 993 developed a cardiac irregularity and cessation of the heart beat during operation. An injection of 1 c.c. of 1:1,000 adrenalin intracardially was followed by recovery; Dog 636 was rather dyspneic for twenty-four hours after the second operation; Dog 621 exhibited marked dyspnea associated with an extensive subcutaneous emphysema on the left side, both persisting for twenty-four hours.

A tendency to gastric dilatation immediately following phrenic nerve paralysis necessitated decreasing the intratracheal positive pressure and in a few instances required postoperative aspiration of air from the stomach. The diaphragm was elevated and immobile when crushed or sectioned.

The sequence and interval between operations varied. In several dogs only one lobe was removed at the first operation, and two lobes at the second operation. In the majority of the animals, however, the sequence was reversed, the larger amount of lung being removed at the first operation. In general this latter procedure was more easily tolerated.

The interval between operative stages varied from three weeks to four months. If, following the first stage, the animal remained in a good nutritional state, and without complications, the second stage was as well tolerated in three weeks as in four months.

TABLE III  
EFFECT OF OBLITERATION OF RESIDUAL-PLEURAL SPACE FOLLOWING REDUCTION OF FUNCTIONING LUNG

REDUCTION OF PLEURAL SPACE	NO. OF DOGS	IMMEDIATE EFFECTS	PHYSICAL AND PHYSIOLOGICAL EFFECTS	GROSS PATHOLOGY	MICROSCOPIC PATHOLOGY
Permanent	11	<ol style="list-style-type: none"> <li>1. Temporary dilatation of stomach on paralysis of phrenic nerve</li> <li>2. No cardiac embarrassment</li> <li>3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax</li> </ol>	<ol style="list-style-type: none"> <li>1. Diaphragms elevated and immobile</li> <li>2. No dyspnea or cyanosis on exercise excepting one-lobe dogs</li> <li>3. Normal reaction to rarified atmosphere</li> <li>4. Healthy</li> <li>5. Change of respiration from abdominal to thoracic type</li> <li>6. No cardiac embarrassment</li> <li>7. EKG normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Adhesions between lung and incision</li> <li>2. Moderate overdistention of lung</li> <li>3. Upper lobe herniation through mediastinum in one-lobe dogs</li> <li>4. Lung spongy in appearance; honey-combed on section</li> <li>5. Heart normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Definite emphysema found in one-lobe dogs</li> <li>2. Dilatation and disruption, especially the alveolar ducts and sacs in one-lobe dogs</li> <li>3. Bronchi dilated, particularly terminal portions</li> <li>4. Some breakdown and stretching of alveolar walls in one-lobe dogs</li> <li>5. No connective or elastic tissue increase; some disruption in one-lobe dogs</li> </ol>
Partial permanent and temporary	9	<ol style="list-style-type: none"> <li>1. Temporary dilatation of stomach on paralysis of phrenic nerve</li> <li>2. No cardiac embarrassment</li> <li>3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax</li> </ol>	<ol style="list-style-type: none"> <li>1. Temporary elevation of diaphragm with regeneration in 2 or 3 mo.</li> <li>2. No dyspnea or cyanosis on exercise</li> <li>3. Normal reaction to rarified atmosphere</li> <li>4. Healthy</li> <li>5. No significant change in type of respiration</li> <li>6. No cardiac embarrassment</li> <li>7. EKG normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Adhesions between lung and incision</li> <li>2. Increased overdistention of lung</li> <li>3. Upper lobe herniation through mediastinum in one-lobe dogs</li> <li>4. Lung spongy in appearance; honey-combed on section</li> <li>5. Heart normal</li> </ol>	<ol style="list-style-type: none"> <li>1. No emphysema</li> <li>2. Dilatation of terminal respiratory units</li> <li>3. Bronchi dilated, particularly terminal portions</li> <li>4. Some stretching of alveolar walls—no disruption</li> <li>5. No connective or elastic tissue increase; stretching but less disruption in one-lobe dogs</li> </ol>
Temporary	6	<ol style="list-style-type: none"> <li>1. Temporary dilatation of stomach on paralysis of phrenic nerve</li> <li>2. No cardiac embarrassment</li> <li>3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax</li> </ol>	<ol style="list-style-type: none"> <li>1. Temporary elevation of diaphragm with regeneration in 2 or 3 mo.</li> <li>2. No dyspnea or cyanosis on exercise</li> <li>3. Normal reaction to rarified atmosphere</li> <li>4. Healthy</li> <li>5. Change of respiration from abdominal to thoracic type during paralysis</li> <li>6. No cardiac embarrassment</li> <li>7. EKG normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Adhesions between lung and incision</li> <li>2. Marked overdistention of lung</li> <li>3. Lung spongy in appearance; honey-combed on section</li> <li>4. Heart normal</li> </ol>	<ol style="list-style-type: none"> <li>1. No emphysema</li> <li>2. Dilatation of terminal respiratory units</li> <li>3. Bronchi dilated, particularly terminal portions</li> <li>4. Some stretching of alveolar walls—no disruption</li> <li>5. No connective or elastic tissue increase; stretching but no disruption</li> </ol>



TABLE IV  
COMPARATIVE STUDY OF VARYING DEGREES OF REDUCTION OF FUNCTIONING LUNG TISSUE:

REDUCTION TO	MILTIPOD	NO. OF DOGS	IMMEDIATE EFFECTS	LATE EFFECTS	CAUSE OF DEATH			
					OPERA- TIVE	DIS- TEMPER	OTHER CAUSES	SACRI- FICED
Three lobes	Resection	12	No cardiorespiratory embarrassment except Dog 993; tendency to gastric dilatation upon paralysis of diaphragm; slight dyspnea	Resectio: Dyspnea { at rest—none { on exertion—slight Rarified atmosphere—normal EKG—normal Nutritional state—good Air passages and cells—diluted	4	2		6
	Resection	4	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; slight dyspnea	Dyspnea { at rest—none { on exertion—slight EKG—normal Air passages and cells—diluted				3
	Resection and stenosis	4	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; slight dyspnea	Dyspnea { at rest—none { on exertion—slight Rarified atmosphere—almost normal EKG—normal Air passages and cells—diluted		2		2
One lobe	Resection	1	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; Dog 867, dyspnea for twenty-four hr.	Dyspnea { at rest—none { on exertion—moderate EKG—temporary cardiac irregularity Dilatation of esophagus—caused death			1	
	Resection and stenosis	5	No cardiorespiratory embarrassment; tendency to gastric dilatation upon paralysis of diaphragm; Dog 621, dyspnea for twenty-four hr.	Dyspnea { at rest—none { on exertion—moderate Rarified atmosphere—almost normal EKG—normal Compensatory emphysema—present		1		3

TABLE III  
EFFECT OF OBLITERATION OF RESIDUAL-PLEURAL SPACE FOLLOWING REDUCTION OF FUNCTIONING LUNG

REDUCTION OF PLEURAL SPACE	NO. OF DOGS	IMMEDIATE EFFECTS	PHYSICAL AND PHYSIOLOGICAL EFFECTS	GROSS PATHOLOGY	MICROSCOPIC PATHOLOGY
Permanent	11	<ol style="list-style-type: none"> <li>1. Temporary dilatation of stomach on paralysis of phrenic nerve</li> <li>2. No cardiac embarrassment</li> <li>3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax</li> </ol>	<ol style="list-style-type: none"> <li>1. Diaphragms elevated and immobile</li> <li>2. No dyspnea or cyanosis on exercise excepting one-lobe dogs</li> <li>3. Normal reaction to rarified atmosphere</li> <li>4. Healthy</li> <li>5. Change of respiration from abdominal to thoracic type</li> <li>6. No cardiac embarrassment</li> <li>7. EKG normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Adhesions between lung and incision</li> <li>2. Moderate overdistention of lung</li> <li>3. Upper lobe herniation through mediastinum in one-lobe dogs</li> <li>4. Lung spongy in appearance; honey-combed on section</li> <li>5. Heart normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Definite emphysema found in one-lobe dogs</li> <li>2. Dilatation and disruption, especially the alveolar ducts and sacs in one-lobe dogs</li> <li>3. Bronchi dilated, particularly terminal portions</li> <li>4. Some breakdown and stretching of alveolar walls in one-lobe dogs</li> <li>5. No connective or elastic tissue increase; some disruption in one-lobe dogs</li> </ol>
Partial permanent and temporary	9	<ol style="list-style-type: none"> <li>1. Temporary dilatation of stomach on paralysis of phrenic nerve</li> <li>2. No cardiac embarrassment</li> <li>3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax</li> </ol>	<ol style="list-style-type: none"> <li>1. Temporary elevation of diaphragm with regeneration in 2 or 3 mo.</li> <li>2. No dyspnea or cyanosis on exercise</li> <li>3. Normal reaction to rarified atmosphere</li> <li>4. Healthy</li> <li>5. No significant change in type of respiration</li> <li>6. No cardiac embarrassment</li> <li>7. EKG normal</li> </ol>	<ol style="list-style-type: none"> <li>1. Adhesions between lung and incision</li> <li>2. Increased overdistention of lung</li> <li>3. Upper lobe herniation through mediastinum in one-lobe dogs</li> <li>4. Lung spongy in appearance; honey-combed on section</li> <li>5. Heart normal</li> </ol>	<ol style="list-style-type: none"> <li>1. No emphysema</li> <li>2. Dilatation of terminal respiratory units</li> <li>3. Bronchi dilated, particularly terminal portions</li> <li>4. Some stretching of alveolar walls—no disruption</li> <li>5. No connective or elastic tissue increase; stretching but less disruption in one-lobe dogs</li> </ol>
Temporary	6	<ol style="list-style-type: none"> <li>1. Temporary dilatation of stomach on paralysis of phrenic nerve</li> <li>2. No cardiac embarrassment</li> <li>3. Tendency to respiratory embarrassment until reduction of surgical pneumothorax</li> </ol>	<ol style="list-style-type: none"> <li>1. Temporary elevation of diaphragm with regeneration in 2 or 3 mo.</li> <li>2. No dyspnea or cyanosis on exercise</li> <li>3. Normal reaction to rarified atmosphere</li> <li>4. Healthy</li> <li>5. Change of respiration from abdominal to thoracic type during paralysis</li> <li>6. No cardiac embarrassment</li> </ol>	<ol style="list-style-type: none"> <li>1. Adhesions between lung and incision</li> <li>2. Marked overdistention of lung</li> <li>3. Lung spongy in appearance; honey-combed on section</li> <li>4. Heart normal</li> </ol>	<ol style="list-style-type: none"> <li>1. No emphysema</li> <li>2. Dilatation of terminal respiratory units</li> <li>3. Bronchi dilated, particularly terminal portions</li> <li>4. Some stretching of alveolar walls—no disruption</li> <li>5. No connective or elastic tissue increase; stretching but no disruption</li> </ol>

pneumothorax observed after the immediate postoperative period. In the previous work referred to spontaneous pneumothorax was observed on numerous occasions when reduction of the lung function was accomplished by bronchial stenosis. It was noted on the side of greatest collapse. We had no case of spontaneous pneumothorax, although it was suspected in Dog 687. Large emphysematous bullae were found at autopsy in several instances however. These were in the one- (15 per cent) or two- (30 per cent) lobe dogs, No. 695 in particular. In one instance a large bulla was found in a three-lobe (38.7 per cent) dog (No. 886).

Permanent bronchial closure was routinely obtained by the method described. At autopsy the stumps were firmly healed, although suture material persisted in some cases.

*Cardiac Phenomena.*—No cardiac irregularities were noted except in Dog 867 as described above. The electrocardiograms were normal. At autopsy, no gross cardiac abnormalities were found.

*Diaphragms.*—Frequent fluoroscopic and roentgenologic examinations were made in order to note intrathoracic changes and recovery of diaphragmatic function. The diaphragms were elevated and immobile or the motion paradoxical in cases of unilateral paralysis. Fluoroscopic and x-ray studies of the diaphragms showed the following: (1) In permanent paralysis the diaphragm was usually elevated to the eighth interspace. (2) In temporary paralysis, after recovery of function, the elevation was usually at the ninth rib. (3) Where no paralysis was produced the diaphragm was usually located at the tenth rib. In general the elevation varied directly with the degree of reduction of lung function. When temporarily paralyzed diaphragmatic function returned in two to three months. Normal respiration in the dog is largely abdominal in type. As paralysis was carried out thoracic breathing was more noticeable. When both phrenics were interrupted breathing seemed changed completely, the dog appeared dyspneic, respiration labored and diminished. These dogs did not pant nor were they cyanotic even when exercising. The nutritional state remained good throughout the experimental period with two exceptions (Dogs 30 and 612). In many instances the animals gained weight. An open empyema was present in Dog 637, but this did not affect the dog's weight.

On physical examination there was dullness to percussion over the atelectatic lobes. Where the lung function was reduced to one lobe (15 per cent) the heart was usually palpable immediately beneath the chest wall on the opposite side. This finding was verified on fluoroscopy and at autopsy. The remainder of the chest was usually hyper-resonant.

*Fluoroscopy* revealed a decreased density of the overdistended lung and the deviation of the mediastinum with its contents, especially in one-lobe dogs, the superior portion often reaching the opposite chest wall. In several cases the right heart seemed slightly dilated.

## LATE EFFECTS

*Respiratory Reserve.*—While at rest there were no manifestations of diminished respiratory reserve. Dogs 621 and 30, after having permanent paralysis of the diaphragms and reduction of lung function to 15 per cent (one lobe), had an apparent increase in respiratory effort. An interesting observation was their inability to pant. They were never found to be cyanotic.

TABLE V  
RESPIRATORY RESERVE AT REST AS DETERMINED BY REDUCTION OF  
ATMOSPHERIC PRESSURE

STANDARD ATMOSPHERIC PRESSURE		CONDITION OF ANIMAL AND PER CENT OF FUNCTIONING LUNG	NO. OF DOG	ALTITUDE TOLERATED	TIME OF ASCENT (MIN.)	AVERAGES	
ALTITUDE (FT.)	PRESSURE (MM. HG)					ALTITUDE (FT.)	PRESSURE (MM. HG)
0	760.0	Normal (6 lobes) 100%	1	30,500	10	30,400	221.6
1,000	733.0		2	30,500	10		
5,000	632.4		3	29,500	10		
10,000	522.6		4	32,000	8		
15,000	428.8		4	29,500	11		
20,000	349.2	3 lobes 38%	917	32,000	6	30,000	225.6
25,000	282.0		993	32,000	7		
30,000	225.6		3	25,000	7		
35,000	178.7		637	31,000	9		
40,000	140.7		871	30,000	9		
		2 lobes 23%	636	27,500	4	26,000	269.8
			869	24,500	6		
		1 lobe 15%	635	26,500*	5	25,833	272.0
			621	25,000†	6		
			695	26,000	10		

\*Failed to recover.

†Did not become unconscious.

While at rest the dogs were put into an evacuation chamber and subjected to rapid diminution of the atmospheric pressure. The results of these tests are presented in Table V. The reduction in atmospheric pressure is indicated in mm. of Hg and the corresponding altitude levels.<sup>8</sup> No appreciable increase in respiratory effort was noted in dogs which had a marked reduction of functioning lung. In general they were able to tolerate almost as much decrease in atmospheric pressure as were normal control dogs.

The dogs tolerated moderate exercise very well. Dogs which ran about much or were excited did not become cyanotic. Dog 869, referred to in Table II, Group IV, was quite dyspneic on exercise. He was able to tolerate a pressure of only 288.2 mm. of Hg (24,500 feet) in the evacuation chamber.

*Pneumothorax.*—Partial obliteration of the surgical pneumothorax immediately after the operation eliminated early respiratory embarrassment and contributed much toward lowering the operative mortality. It is not likely that all the residual air was removed, but in no dog was

In general, x-rays agreed with fluoroscopic findings. Iodized oil injections were made to outline the tracheobronchial tree in its altered status. (Figs. 2 and 3.)



Fig 4—Dog 687 Autopsy specimen showing reduction of function to right upper lobe (15 per cent of normal) showing marked overdistention with herniation into the left chest.

In all two- or three-lobe dogs the mediastinal structures remained in the midline, whereas, in one-lobe dogs the heart was always deviated to the opposite side. There was some rotation of the air passages as demonstrated by the bronchograms.



A.

B.

Fig 2—Dog 867 before (A) and after (B) introduction of iodized oil. The lung function had been reduced by bilateral operation to the two upper lobes (30 per cent of normal).



A.

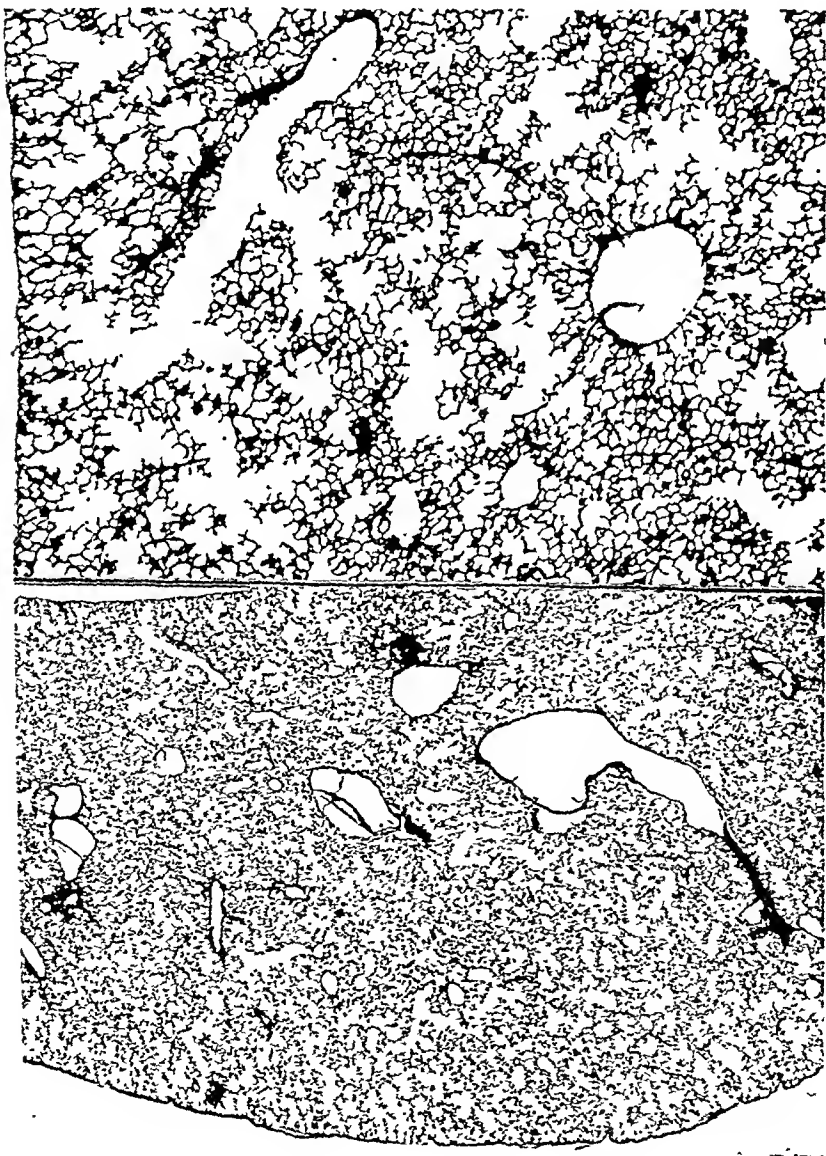
B.

Fig 3—Dog 621. Bronchograms. A, After reduction of function to three lobes (38.7 per cent of normal) by bilateral operation. B, after further reduction of function to the right upper lobe (15 per cent of normal) by bronchial stenosis. Bilateral permanent paralysis of diaphragms.

Where only one lobe remained there was herniation of the lung into the opposite pleural cavity (Fig. 4). This was accompanied by deviation of the heart. There was no demonstrable evidence of hypertrophy or dilatation of the cardiac chambers. The diaphragms were definitely elevated in cases of paralysis.

The lung had a spongy appearance and the alveoli were visible grossly. In several cases a bullous emphysema was seen.

On ent section the lung showed a gross dilatation of the entire bronchial tree.



A.

B.

Fig. 4 and B.—Dog 917. Bilateral temporary paralysis of diaphragm. Microscopic appearance of aerated lung three months after reduction of lung function to three lobes. (Ab. 7 per cent). Note dilatation of terminal respiratory units and similarity to Dog 3 in Fig. 5. ( $\times 7$  and  $\times 20$ .)

## PATHOLOGY

*Gross.*—The remaining inflated lung was usually found adherent to the healed lines of incision. As a rule there was no fluid in the pleural space although a few cubic centimeters were found in some dogs. The lungs routinely showed overdistention, the extent dependent upon two factors: paralysis of the diaphragm and the degree of reduction of functioning lung tissue. This was most extreme in one-lobe dogs and in those instances where the diaphragms were temporarily paralyzed.



Fig. 5 A and B.—Dog 3. Bilateral permanent paralysis of diaphragm. Microscopic appearance of aerated lung three months after reduction of lung function to three lobes (38.7 per cent). Note dilatation of terminal respiratory units. No emphysema demonstrable. Magnification  $\times 7$  and  $\times 20$ .



respiratory pores of the alveolar walls were larger, somewhat distorted and more numerous than normal. The elastic and fibrous tissue elements although often somewhat stretched were not found to be disrupted.

The two-lobe group showed similar pathologic changes with possibly slightly more distention of the individual alveoli, with more marked distention of some of the alveolar ducts and sacs.

The one-lobe dogs showed more severe changes, apparently most severe in animals with permanent paralysis of the diaphragm. There was dilatation of the respiratory bronchioles, alveolar ducts and sacs with a breakdown of the alveolar walls under the pleura. The alveolar walls in some areas were thinned into long avascular strands forming large fibrous vesicles (Fig. 7 A and B). The breakdown was not primarily in the alveoli located immediately beneath the pleura but in the terminal respiratory units, i.e., the alveolar ducts and sacs. Many counts of the alveoli per microscopic field reveal considerable variation among dogs of a group. Averaging all groups one finds the total alveoli per field reduced to approximately one-half the normal.

We are of the opinion that this marked dilatation of the terminal air passages does not represent true emphysema as some authors believe, since the capillary, elastic, and connective tissue fibers are intact.

The walls of the alveolar duct between the alveolar sacs and alveoli are made up of muscle cells, elastic and collagenous fibers.<sup>9</sup> In their sections these appear as short knobs or clubs running parallel to the long axis of the duct. These have been described erroneously as pathologic "clubbings."<sup>2</sup>

#### CLINICAL APPLICATION

Within the last decade marked improvement has been effected in the management of intrathoracic operations. This has been especially noticeable in the resection of lung tissue for neoplastic and inflammatory diseases. Whereas lobectomy for bronchiectasis was once fraught with grave danger, now it is accomplished with relatively little risk. Total pneumonectomy, unsuccessful prior to Graham's<sup>10</sup> first case in 1933, although an operation less safe than lobectomy, is being successfully performed in increasing numbers.

Very frequently, however, the distribution of the lesion in bronchiectasis, includes more than one lobe on one or both sides of the chest. The problem confronting the surgeon has been not only whether the general condition of the patient warranted operation, but how much lung tissue could be safely resected and which side should be resected first. Another disputed point concerns the resultant pleural space. Should the diaphragm be paralyzed temporarily or permanently, if at all, in order to obliterate better the space formerly occupied by the resected lung tissue? Also what effect if any would diaphragmatic paralysis

\*We wish to express our appreciation to Dr. Clayton G. Loosli for his criticism and instruction concerning the microscopic changes of the lungs.

## MICROSCOPIC PATHOLOGY

In general, all sections revealed a dilatation of the air passages. This varied from slight degrees in the larger bronchi to a more extreme degree in the terminal respiratory bronchioles, alveolar ducts and sacs. This dilatation was evident in three-lobe dogs, but we could find little to differentiate animals having permanent paralysis of the diaphragm (Fig. 5 *A* and *B*) from those having the temporary type (Fig. 6 *A* and *B*). Some sections showed diminution in the number of capillaries. The

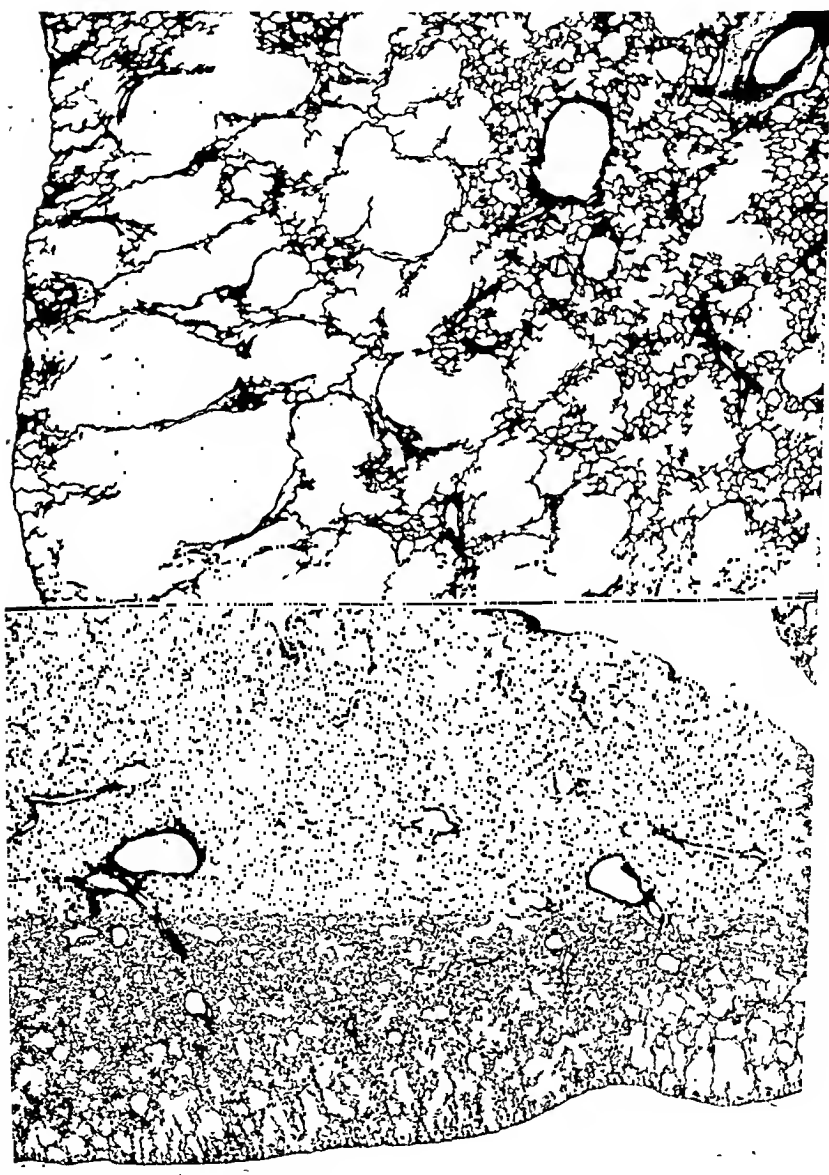


Fig. 7 *A* and *B*.—Dog 30. Bilateral permanent paralysis of diaphragm. Microscopic appearance of acrated lung one month after final reduction to one lobe (15 per cent). Note peripheral distribution of dilatation of terminal respiratory units. Definite emphysematous change in alveolar ducts and sacs. ( $\times 7$  and  $\times 20$ .)

respiratory reserve remained following further reduction to 15 per cent so that the animals were able to tolerate moderate exercise and reduction of atmospheric pressure to almost the limit of normal dogs (25 to 30,000 feet).

2. Bilateral temporary or permanent paralysis of the diaphragm was well tolerated whether the lung function was one lobe or three lobes. Compensatory alterations of the lung from overdilatation were of about the same degree in temporary or permanent paralysis but different in distribution. In permanent paralysis these changes were more peripheral and there was more tendency to bullae formation. In the temporary type the alterations were more evenly distributed.

3. In the absence of complications following the above procedures, the animals remained in a healthy state for the duration of the experiments; that is, six to twelve months.

4. From the above findings it would appear that temporary paralysis of the diaphragm is a justifiable procedure in the human being. In bilateral operations it seems advisable that sufficient time elapse between stages for re-establishment of the diaphragmatic function and improvement of the patient's general health.

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exert on the compensatory changes developing as a result of overdistention of the remaining functioning lung? Another much debated question is whether a thoracoplasty should accompany or follow total pneumonectomy. This latter also applies to the immediate postoperative course as well as to the effect on the resultant alteration in cardio-respiratory function due to overdistention and resultant compensatory alteration of the remaining functioning lung.

*Resection of Lung Tissue.*—The above-described experiments demonstrate that a large part of the lung may be removed with safety, without materially influencing the cardiorespiratory function. When tested by exercise or by reduced atmospheric pressure, the respiratory reserve of dogs with three lung lobes (38.7 per cent) remaining, compared favorably with that of normal animals, while the reserve of one-lobe dogs (15 per cent) was only slightly lowered.

The interval between operations and especially the general condition at the time of the operation were of definite significance. Suffice it to say that sufficient time should elapse between stages to insure adequate return of general resistance with little evidence of toxic manifestation remaining. This period may vary from six weeks to six months.

Another factor of importance was the amount of lung resected at each operation. The above results would indicate that the side of greatest involvement should be resected first, lesser amounts of lung tissue being removed at the second operation.

*Diaphragmatic Paralysis.*—Obliteration of the residual pleural space following lobectomy or bilobectomy may be more easily accomplished by paralyzing the diaphragm. When obliteration is complete and maintained within twenty-four hours after operation, primary healing is encouraged and the convalescence made smoother. A temporary type of paralysis is the more advisable since it has all the advantages of the permanent type immediately after operation and function may be expected to return within two months or by the time the second operation is made. The temporary type is also desirable from the standpoint of compensatory overinflation of the remaining lung. This change is thus more evenly distributed and not as exaggerated at the periphery of the lung. In this regard, however, compensatory overdistention appeared not to influence greatly the function of the lung tissue since one-lung (15 per cent functioning) dogs with or without bilateral diaphragmatic paralysis exhibited no dyspnea or cyanosis while at rest and tolerated reduction of atmospheric pressure equally well and almost within normal limits. On exercise they were mildly dyspneic.

#### SUMMARY

1. Bilateral resection of as much as 62 per cent of the total lung tissue within a period of three weeks was well tolerated in normal dogs, when no complications occurred after the first operation. Sufficient

respiratory reserve remained following further reduction to 15 per cent so that the animals were able to tolerate moderate exercise and reduction of atmospheric pressure to almost the limit of normal dogs (25 to 30,000 feet).

2. Bilateral temporary or permanent paralysis of the diaphragm was well tolerated whether the lung function was one lobe or three lobes. Compensatory alterations of the lung from overdilatation were of about the same degree in temporary or permanent paralysis but different in distribution. In permanent paralysis these changes were more peripheral and there was more tendency to bullae formation. In the temporary type the alterations were more evenly distributed.

3. In the absence of complications following the above procedures, the animals remained in a healthy state for the duration of the experiments; that is, six to twelve months.

4. From the above findings it would appear that temporary paralysis of the diaphragm is a justifiable procedure in the human being. In bilateral operations it seems advisable that sufficient time elapse between stages for re-establishment of the diaphragmatic function and improvement of the patient's general health.

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## THE EFFECT OF REPLACEMENT THERAPY IN EXPERIMENTAL SHOCK

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IT HAS been known for many years that a reduction of the effective blood volume is an essential feature of shock regardless of cause. Recently considerable attention has been directed to the pathologic changes which occur in the tissues in shock. These consist principally of marked diffuse congestion of capillaries and venules in visceral areas, especially the lungs, liver, kidneys, and gastrointestinal tract. The relation of these pathologic changes to the reduced blood volume and the significance of this relationship in the treatment of experimental shock due to severe thermal trauma constitute the subject of this paper.

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The present study was designed to correlate the physiologic effects of fluid replacement with the pathologic changes in shock. Are these

Presented at the meeting of the Society of University Surgeons at St. Louis, Mo., Feb. 14 and 15, 1941.

## THE EFFECT OF REPLACEMENT THERAPY IN EXPERIMENTAL SHOCK

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tissue changes a consequence of the reduced blood volume or are they due to some factor, such as a toxin absorbed from the site of injury which produces generalized capillary injury irrespective of the level of the blood volume? If the pathologic changes are a consequence of the lowered blood volume, it should be possible to prevent them by restoring the blood volume to normal. This has been attempted both in the early and late stages of experimental shock due to thermal trauma.

The experimental procedure and methods used were the same as has been described in detail previously.<sup>1</sup> Large mongrel dogs were used in all the experiments. Shock was induced by thermal trauma. Determinations of the pulse, blood pressure, hematocrit, plasma volume, hemoglobin, and serum proteins were made before and at varying intervals after the injury. The experiments were divided into three groups. In

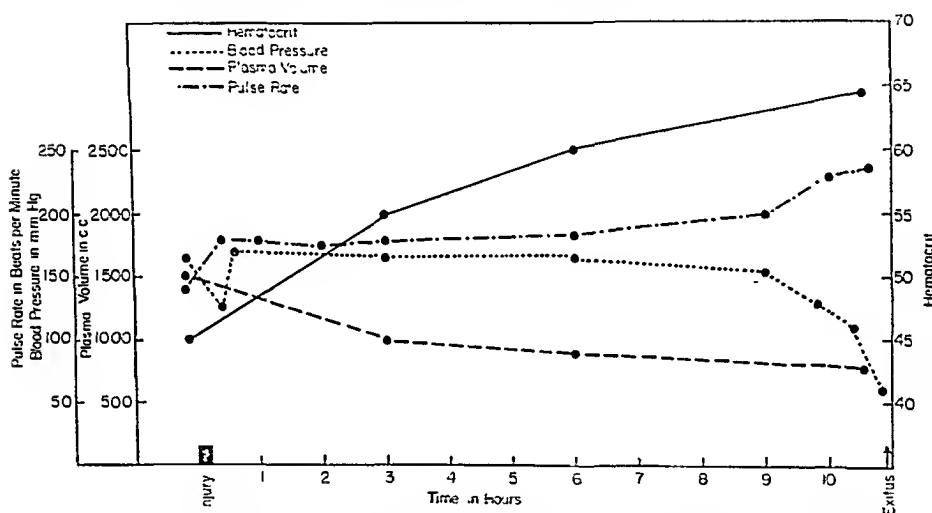


Fig. 1.—The typical course of the changes in hematocrit, blood pressure and plasma volume in experimental shock due to thermal trauma.

one the effects of treatment in late shock were observed. In another the response and end results of a single infusion of plasma or saline solution in early shock were determined and finally, the effects of continuous infusions of plasma were studied. The results are tabulated in Table I. Individual experiments representative of each group are shown in the accompanying graphs.

#### TREATMENT IN LATE SHOCK

The inefficacy of treatment in late shock is well known. It has been thought that at this stage fluid leaked out of the vascular system through damaged capillaries so rapidly that the blood volume could not be restored to normal. That this is not the case is shown in Experiments 1, 2, and 3 (Table I). In these experiments therapy was instituted after the blood pressure had fallen, indicating an advanced degree of shock.

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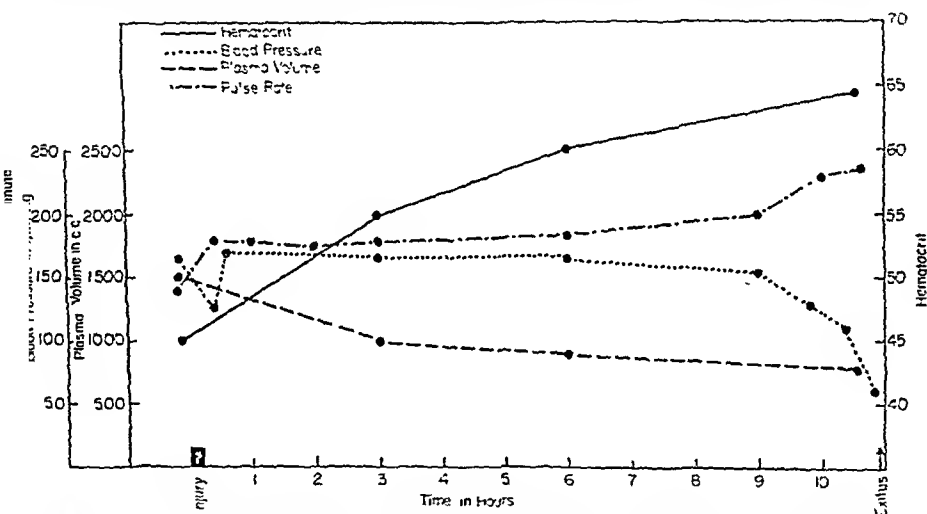


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6	17.4	Plasma 200 c.c.	Before injury 4½ hr. after injury 1 hr. after treatment (4½ hr. after injury) 2½ hr. after treatment (7 hr. after injury)	130 180 150 150 210	160 140 150 150	48.3 65.8 53.0 58.0	762 561 780 600	16.5 20.0 17.8 19.7	5.9 6.8 7.7 6.4	Marked improvement with plasma but this was not maintained. No dilution of serum protein. Animal sacrificed.	No striking alteration of the usual tissue changes
7	21.3	Plasma 200 c.c. 1 hr. after injury	Before injury ½ hr. after injury 1 hr. after treatment (3 hr. after injury) 5 hr. after treatment (6 hr. after injury)	128 130 150 160	130 130 140 130	43.1 52.0 57.2 55.5	1,335 900 865	14.1 19.0	6.9 6.8 6.8	Single infusion inadequate to maintain plasma volume.	No striking alteration of the usual tissue changes
8	21.4	Plasma 400 c.c. Saline solution 500 c.c. Continuous infusion of plasma started ½ hr. after injury after injury (see Fig. 6)	Before injury 4 hr. after plasma (5 hr. after injury) 6½ hr. after injury (1 hr. after saline) 8 hr. after injury	150 150 160 190	140 140 150 150	51.7 46.9 39.8 51.5	872 945 775		6.3 5.4 4.3	Marked dilution of serum protein after saline solution.	Considerable amelioration of usual late tissue changes (see text for discussion)
9	18.8	950 c.c. Plasma (protein 2.5 Gm. per cent). Continuous infusion begun 1 hr. after injury after injury (see Fig. 7)	Before injury ½ hr. after injury 6 hr. after injury 8½ hr. after injury	160 150 140	160 140 140	54.2 59.0 54.2	802 710 638		6.3 6.3 6.5	Slight fall in plasma volume but general condition of animal well sustained. Replacement not quite adequate.	Marked amelioration of tissue changes (see text for details)
10	21.3	700 c.c. Plasma (protein 5.5 Gm. per cent). Continuous infusion begun 2 hr. after injury	Before injury ½ hr. after injury 6 hr. after injury 9 hr. after injury	150 160 150 140	140 140 140 140	45.5 39.6 38.8 36.3	1,370 1,606		6.5 6.3 6.3	Blood volume increased by infusion. No hemoconcentration.	Marked amelioration of tissue changes (see text for details)

The response to a transfusion of whole blood is shown in Fig. 2. Although there was a considerable rise in the blood volume the blood pressure continued to fall and exitus occurred with the blood volume at a nearly normal level. Note that there was no improvement in the hemoconcentration. A somewhat similar response occurred when plasma was used (Fig. 3). Here, however, there was a temporary rise in the blood pressure and considerable improvement of the hemoconcentra-

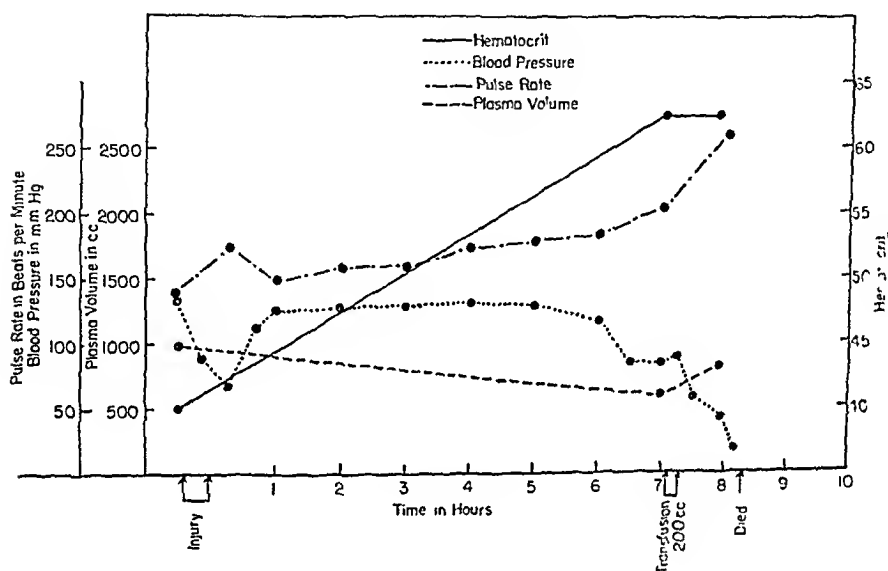


Fig. 2.—The effect of a transfusion of blood in the late stage of experimental shock.

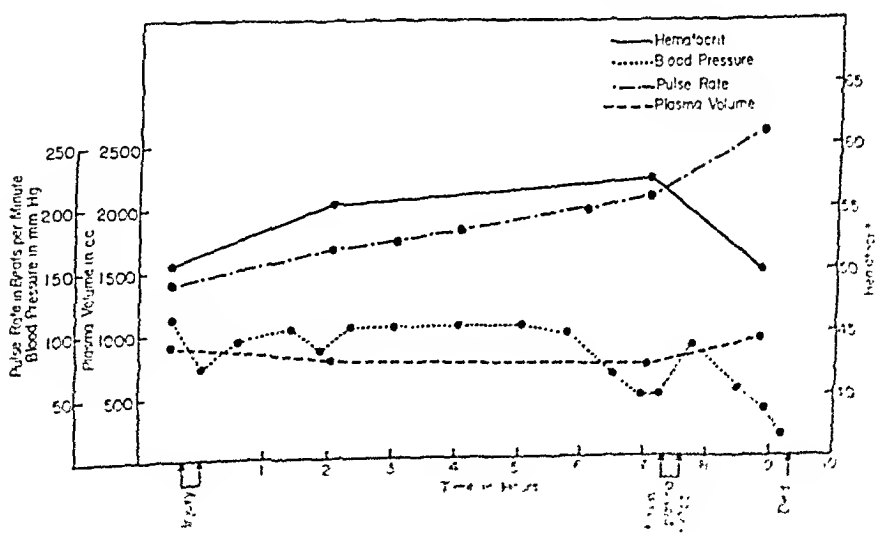


Fig. 3.—The effect of an infusion of plasma in the late stage of experimental shock.

tion. However, death occurred when the plasma volume was normal. Post-mortem examination in Experiments 1, 2, and 3 revealed the usual gross and microscopic changes of late shock. These have been described in detail elsewhere<sup>1</sup> and will not be elaborated on here. Suffice it to say that no alteration of the usual tissue changes which follow prolonged anoxia could be demonstrated. It is concluded that therapy instituted in the very late stages of shock has no demonstrable effect on the pathologic changes in the tissues and even though it restores the blood volume to normal the course of the shock is not greatly altered. Under these circumstances death may occur with a normal plasma volume (Experiment 3). This suggests that once well established the pathologic changes in the tissues are irreversible and therapy, to be effective, must be instituted before such generalized tissue injury occurs.

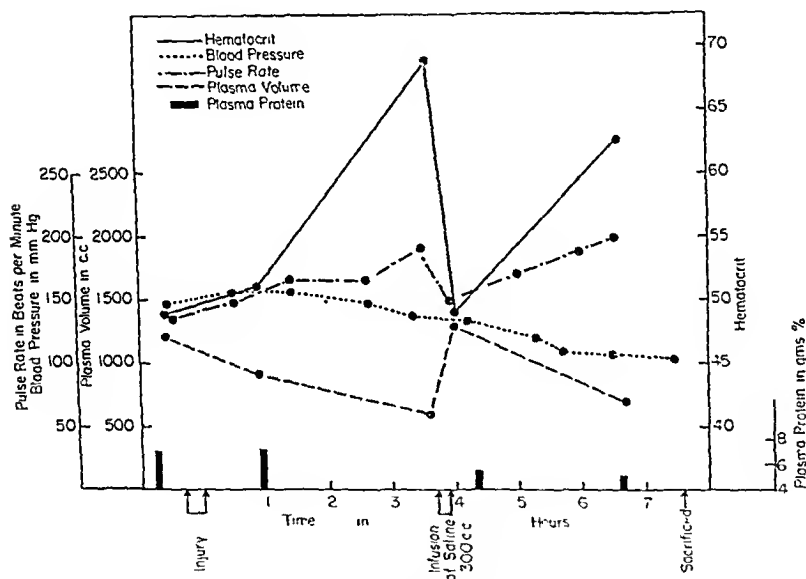


Fig. 4.—The effect of an infusion of saline and bicarbonate solution in experimental shock.

#### TREATMENT IN EARLY SHOCK

In Experiments 4, 5, 6, and 7 therapy was started shortly after the plasma volume had fallen. An amount of fluid calculated to restore the volume to normal was given. The comparative efficacy in this respect of a nonecolloidal solution and plasma is shown in Figs. 4 and 5. When saline solution was given, there was a marked improvement in the hemoconcentration and a rise in the plasma volume. However, this was accompanied by such a dilution of the blood that the concentration of serum proteins fell to edema levels. The danger of using saline solutions in shock has been emphasized before. Beard and Blalock<sup>4, 5</sup> observed that animals which received saline infusions often seemed worse

after the infusion was stopped than if no therapy had been given. This was confirmed in the present study. Moreover, it was found that the pathologic changes in the tissues, particularly edema, seemed more striking following saline infusion than when no therapy was given (Experiments 4 and 5).

The superiority of plasma as a replacement fluid in shock has been demonstrated by a number of investigators.<sup>6-8</sup> Considerable emphasis has been placed on the idea that there is no dilution of the serum proteins, that the osmotic pressure of the blood is not lowered, and that, therefore, the improvement following its use is more permanent than when saline or dextrose solutions are given. It should be emphasized

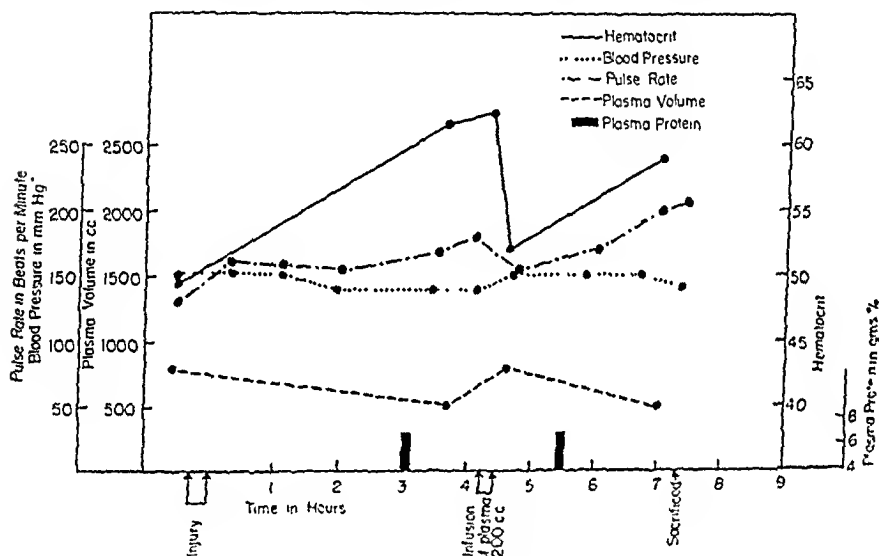


Fig. 5.—The effect of an infusion of plasma in experimental shock

that although the beneficial effects of plasma are considerable, the duration of the improvement following its use in severe thermal trauma was of short duration (Experiments 6 and 7) (Fig. 5). With the important exception that there was no dilution of the plasma proteins, the effect on the blood volume of a single infusion of plasma in severe shock was little different than when saline solution was used. This does not mean that plasma is not greatly superior to saline solution, but it serves to emphasize that repeated infusions of plasma are often necessary. Moreover, on pathologic examination there was no striking change in the appearances of the tissues in animals which received only a single infusion of plasma.

In the final group of experiments<sup>9,10</sup> therapy was instituted early and maintained throughout the experimental period. In Fig. 6 is shown the response to a 400 c.c. infusion of plasma followed by a 500 c.c. infusion of saline solution. Five hours after the injury there was no

hemoconcentration and both the plasma and total blood volumes were normal. The concentration of serum proteins was normal. However, immediately after the infusion of saline solution there was a fall in the hematocrit to subnormal levels and a dilution of the serum proteins. Two hours later the plasma volume was considerably reduced. At post mortem pathologic changes in the viscera were found, but these were less marked than are usually found in experiments of this duration. There was considerable edema of the lungs, but the gastrointestinal tract showed but little variation from the normal. The loss of protein in this experiment merits comment. The infusion of plasma at the rate of 100 c.c. an hour sufficed to maintain the total protein of

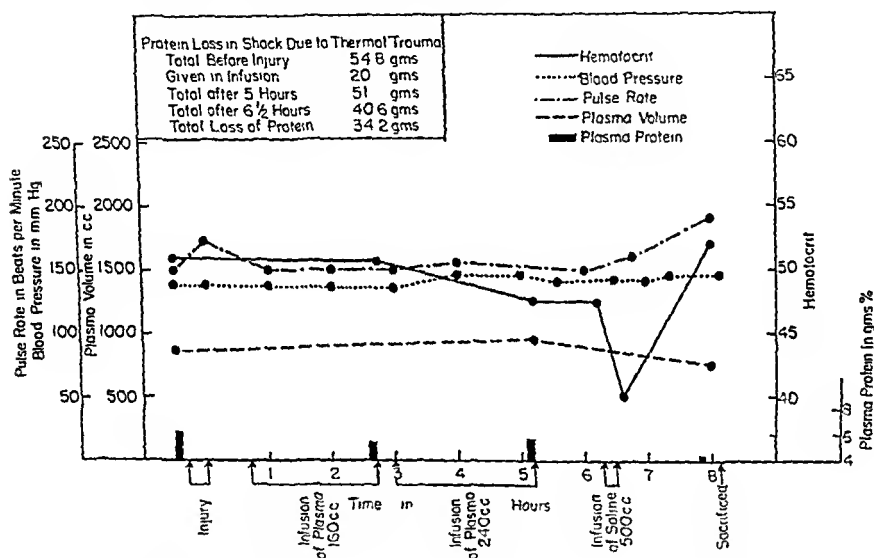


Fig. 6.—The effect of plasma infusion followed by saline infusion in experimental shock.

the body at normal levels for four hours. Despite this amount of replacement, immediately after saline solution was used there was a fall in the total amount of protein as well as a considerable reduction of the concentration of proteins. This, again, serves to demonstrate the dangers of saline solution in shock of this type even when it is used as an adjunct to plasma.

The effects of continuous infusions of plasma were studied in Experiments 9 and 10. In one of these (Fig. 7) an infusion of 950 c.c. of plasma (protein content 2.5 Gm. per cent) was given over a period of seven and one-half hours. This was sufficient to maintain the plasma volume at nearly normal levels throughout the experiment, but there was a progressive dilution of the plasma proteins indicating that the replacement was not quite adequate. In Experiment 10, 700 c.c. of plasma (protein content 5.5 per cent) was given over a period of eight hours.



Not only was this sufficient to maintain the level of the plasma protein but actually it brought about an increase in the plasma volume (Table I). It would appear that to a certain extent the earlier and more adequate the replacement therapy, the less fluid is required and the less extensive is the protein loss. If treatment is delayed until the blood volume has fallen, generalized capillary damage occurs and the possible areas from which fluid may escape are greatly increased. Moreover, if the protein composition of the replacement fluid is greatly lower than that of plasma, this fluid may escape from the blood stream with a higher protein content than when it entered, thereby increasing the rate of protein loss.<sup>4, 5</sup>

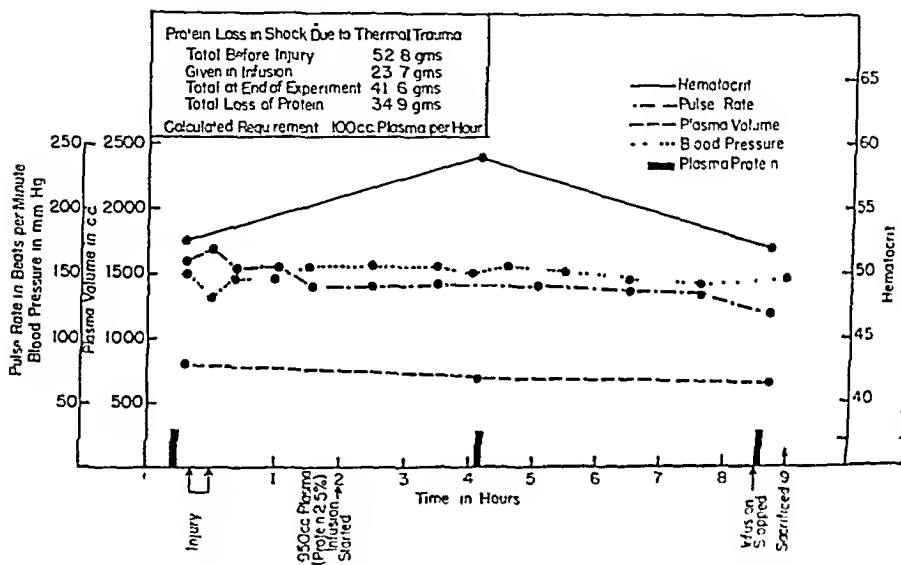


Fig. 7—The effect of a continuous infusion of plasma in experimental shock.

Pathologic examination in Experiments 9 and 10 disclosed very marked amelioration of the usual late tissue changes. Grossly there was no obvious variation from the normal except for slight atelectasis and congestion of the dependent portions of the lower lobes of both lungs and moderate congestion of the kidneys. The entire gastrointestinal tract, liver, pancreas, and adrenals appeared normal. On microscopic examination there was minimal evidence of capillary dilatation in the lungs, kidneys, and adrenals. These changes have been described before as occurring even in the early stages of shock, under the condition of these experiments and probably are due to the use of sodium pentobarbital as the anesthetic. However, the usual marked tissue changes of advanced shock were not present. The liver showed no congestion of the sinusoids or degenerative changes in the cord cells, although in some areas there were collections of polymorphonuclear

leucocytes scattered through the sinusoids. No evidence of edema, congestion, or capillary injury was found in the gastrointestinal tract on microscopic examination. Thus, although it cannot be said that following adequate replacement therapy there is no evidence of generalized capillary injury, there is such a striking amelioration of the usual pathologic changes as to lead us to believe that these are principally the result of anoxia, secondary to the reduction of the blood volume and hence are largely preventable by early and adequate therapy.

The amount of protein necessary to maintain an adequate level in severe shock requires further comment. As shown in Figs. 6 and 7, the total loss of protein in eight to nine hours of severe shock may amount to as much as 35 Gm. If given as plasma in a concentration of 5 Gm. per cent, it would take roughly 80 c.c. of plasma per hour to maintain a normal level, assuming that treatment was started shortly after injury. However, as shown in Fig. 1, the principal reduction of the plasma volume occurs within the first few hours of injury so that if treatment were delayed even for two or three hours, the rate of replacement would necessarily have to be higher to make up the deficit. In the experimental animal with a blood volume of 2.5 liters approximately 75 to 100 c.c. of plasma per hour would seem necessary (Experiments 8, 9, and 10). If we transpose this estimate to the clinic, it means that a severely burned patient weighing 70 kg. would require between 100 to 200 c.c. of plasma per hour for the first ten hours after injury. Although this figure is considerably in excess of the amounts usually used, in a recent clinical study Elman<sup>9</sup> suggested that as much as 1,400 c.c. may be required. It seems likely that the sudden, unexplained collapse of patients in the early stages of severe burns may be due to this enormous reduction of the plasma volume.

How long therapy must be maintained has not been determined in this study. It is hardly practical to do so in the laboratory because of the complicating factor of prolonged anesthesia. On the basis of a recent clinical study<sup>10</sup> it has been suggested that plasma loss may continue for as long as forty hours.

#### SUMMARY

Under the conditions of these experiments, replacement therapy instituted in the late stages of experimental shock has no effect on the pathologic changes in the tissues even though it restores the blood volume to normal. In early shock a single infusion of saline solution, in amount calculated to raise the blood volume to normal, not only is of temporary benefit but causes such a dilution of the plasma proteins that the late tissue changes of shock are accentuated. Under the same circumstances the beneficial effects of a single infusion of plasma are also of only short duration and bring about no alteration of the pathologic

changes. By a continuous infusion of plasma, begun early in the experimental period, the blood volume may be maintained at normal levels and under such circumstances there is a marked amelioration of the late tissue changes in shock. The amounts of plasma necessary to do this are considerably in excess of those generally used in the treatment of burns in patients.

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# REACTIONS TO LOCAL ANESTHETIC AGENTS

## I. EXPERIMENTAL STUDIES WITH PROCAINE

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ALTHOUGH local anesthesia has proved through long use to be a very valuable aid in surgery, in many instances the anesthesia of choice and undoubtedly the safest of all methods of rendering surgery painless, alarming and even fatal reactions sometimes occur. Efforts have been made toward an understanding of these reactions, and suggestions relating to their prevention and treatment have been offered; and yet many problems remain unsolved.

This communication reports some efforts to elucidate a few of these problems. I have been interested in trying to learn something concerning the cause of death, the difference between the "collapse" and the "respiratory failure-convulsive" types of reaction, the influence of the route of administration, the concentration of the injected solution, and the age of the subject upon the toxicity of procaine, the use of local anesthesia during general ether anesthesia, and possible prophylactic and therapeutic aids.

Much is known from experimental and clinical studies concerning the relative merits and inherent dangers of the various members of the group of cocaine-like anesthetics, and it is generally agreed that procaine is the safest and most useful agent for local infiltration or nerve blocking.<sup>1-5</sup> It is also known that although these drugs differ from one another in relative toxicity, the reactions they may evoke are essentially alike. For these reasons and because procaine is the most widely used of these agents, these experiments have been limited to a study of this one drug.

### MATERIALS AND METHODS

Each day a fresh solution was prepared from U.S.P. procaine crystals and distilled water. A 10 per cent solution was used throughout except in the study dealing with the effect of concentration, in which 1 per cent and 0.5 per cent solutions were also used. The dosage of procaine was on a basis of body weight in kilograms. All intravenous injections were made as rapidly as possible. In the paravertebral injections the solution was colored with a minute amount of gentian violet so that the accuracy of the injection could be determined at autopsy. The procaine to which the gentian violet had been added underwent a slight diminution in toxicity as determined by bio-assay with intravenous injections.

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A correction for this was accordingly made. Normal healthy guinea pigs and mongrel dogs were used. That group of guinea pigs which are described as "young" were actively growing animals varying in weight from 300 to 450 Gm. (average 389 Gm.); those described as "old" were one year older than the first group and varied in weight from 500 to 640 Gm. (average 575 Gm.).

Mean arterial blood pressure was measured by a kymographie recording mercury manometer connected with a cannula in the common carotid artery, a small bulb near the cannula filled with citrate solution being used to prevent clotting. Oxygen consumption as well as respiratory rate and minute volume were measured by means of a Sanborn motor-graphic metabolism tester attached to a tracheal cannula. Blood samples were collected from the carotid artery and placed in flasks containing dried potassium and ammonium oxalate.\* This method prevents clotting without causing shrinkage of the erythrocytes. Wintrobe hematocrit tubes were used; proteins were estimated by the falling drop method with the La Motte densimeter; plasma volume was determined with the photoelectric microcolorimetric technique with the azo-blue dye T1824.<sup>6</sup> At least three injections of dye were made in each instance in order to determine accurately the rate of disappearance of the dye. Blood procaine estimations, free and total, were made according to a modification of Bratton and Marshall's<sup>7</sup> method for determination of sulfanilamide, which permitted accurate assay of 0.2 c.c. of blood. Concentration was determined from photoelectric colorimetric readings, a standard curve having been established with procaine solutions of known strength.

#### EXPERIMENTAL OBSERVATIONS AND COMMENTS

When guinea pigs are given a lethal dose or more of procaine subcutaneously, intramuscularly, or by any route where slow absorption presumably takes place, the sequence of events is ordinarily fairly uniform. After an interval of some minutes the animal becomes "groggy," and shortly afterward falls over with diminution or loss of consciousness. Irritative central nervous system phenomena ensue, at first muscular twitchings and purposeless movements and rapidly thereafter generalized convulsions. During this period respirations are ordinarily increased. After a time the convulsions become weaker and the heart stops and respirations cease. Generally but not invariably the last respiratory gasp precedes by a moment or so cessation of the heart beat. Sometimes weak respirations continue momentarily after the heart beat is no longer perceptible. In general, one is impressed by the fact that cardiac and respiratory failure occur almost simultaneously. Occasionally on the approach of death a little froth is seen at the nostrils.

\*One and three-tenths grams of ammonium oxalate and 0.7 Gm. of potassium oxalate in 100 c.c., 0.1 c.c. for each cubic centimeter of blood (Wintrobe).

If a fatal dose is given intravenously, the animal almost immediately falls over as if unconscious, convulsions begin, respirations cease or are replaced by infrequent gasps, and the heart beat rapidly becomes imperceptible. Heart beat and respirations often stop simultaneously. Frequently a weak respiration or two follow cessation of the heart beat as determined by palpation of the chest. Sometimes the reverse is true, and in every instance in which the thorax was opened immediately after cessation of respiration and loss of heart action as determined by palpation, the heart was found to be beating weakly. Whenever death followed an intravenous procaine injection in an animal previously given nembutal or ether, respirations always ceased before the heart beat was no longer palpable. At autopsy, regardless of the route of administration of the procaine, no gross pathologic change was noted. The lungs did not appear edematous.

It was thought advisable to follow graphically certain changes in larger animals. The experiment was as follows: A dog was placed upon the operating table, and with 10 per cent phenol as a local anesthetic, the trachea and one common carotid artery were cannulated. Blood pressure was recorded continuously on a kymograph and pulse and respiratory rates were charted at intervals. Intermittent graphic records of respiratory rate and volume as well as oxygen consumption were made by attaching the tracheal cannula to the metabolism machine. Samples of blood were drawn at intervals for hematocrit, protein, and plasma volume estimations. After a suitable period of normal control observations, procaine was administered. Several experiments are illustrated in Figs. 1, 2, and 3.

In the experiment recorded in Fig. 1, 1,000 mg. of procaine per kilogram of body weight was given subcutaneously; in that recorded in Fig. 2, 700 mg. per kilogram was given subcutaneously at the beginning and the same dose toward the end of the experiment. During the control period there were minor fluctuations in blood pressure, hematocrit, plasma proteins, and plasma volume, greater fluctuations in pulse, and still greater in respiratory rate and minute volume. These variations must be taken into consideration in analyzing the data obtained during the procaine reaction. In these experiments one is impressed by the relative constancy of hematocrit, plasma proteins, and plasma volume. No significant change is noted. It will be observed that the blood pressure tends to rise slightly or moderately after the procaine is administered and to be well maintained until the terminal period of collapse begins, when it drops precipitously to zero accompanied by a sudden cessation of heart beat and respirations. In general, the respiratory rate tends to rise during the reaction, as does the minute respiratory volume, until near the end it suddenly becomes slow and respirations cease. No characteristic change in oxygen consumption is

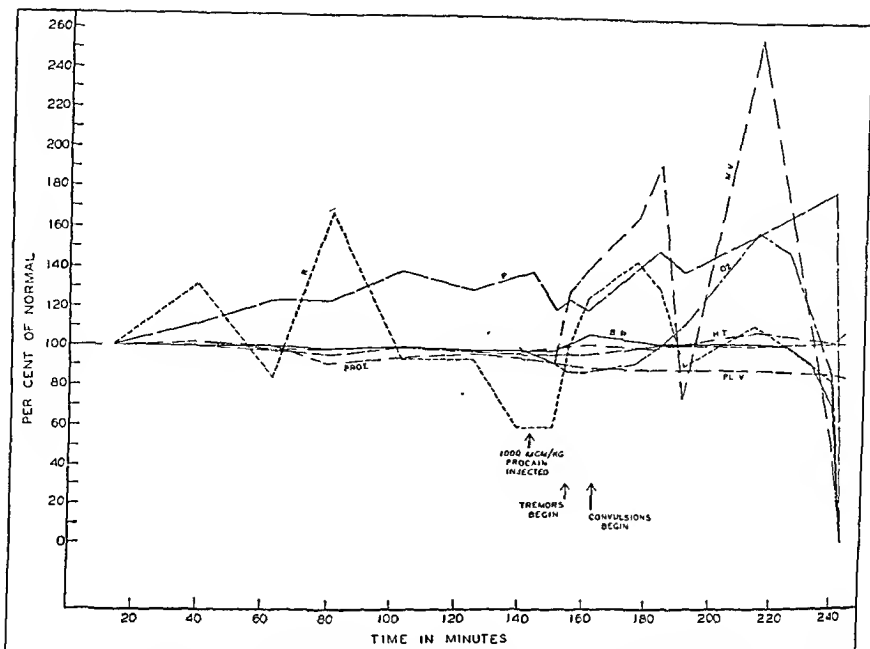


Fig. 1.—Chart showing changes in hematocrit, plasma proteins, plasma volume pulse, blood pressure, respirations, minute volume, and oxygen consumption in a dog during a fatal reaction from procaine injected subcutaneously.

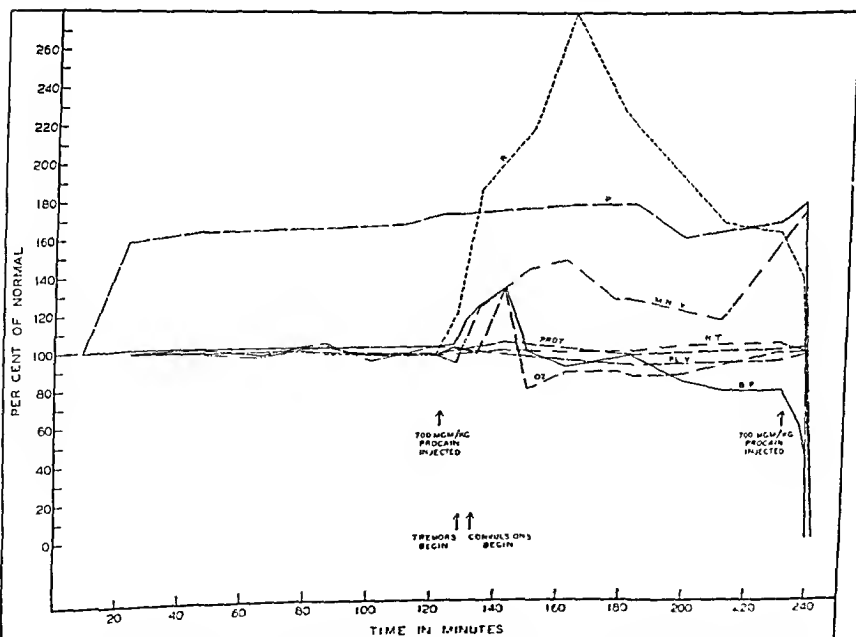


Fig. 2.—Same as Fig. 1. The procaine was injected subcutaneously in two doses.

noted; the increases which occurred seemed related to convulsive movements and restlessness. It will be noted that in the first experiment heart beat and respirations ceased simultaneously and that in the second experiment a few weak respirations persisted for two minutes after pulse and heart beat were no longer perceptible.

In Fig. 3 is recorded an experiment in which increasingly large intravenous doses of procaine were given at intervals. It will be seen that a transient rise in blood pressure follows a very small dose of procaine. After a somewhat larger dose a momentary fall in blood pressure is rapidly succeeded by a rise to a higher than normal level. When a nearly lethal dose is injected, the drop in pressure is continued a little longer; and finally, when a lethal dose is injected a precipitous drop to

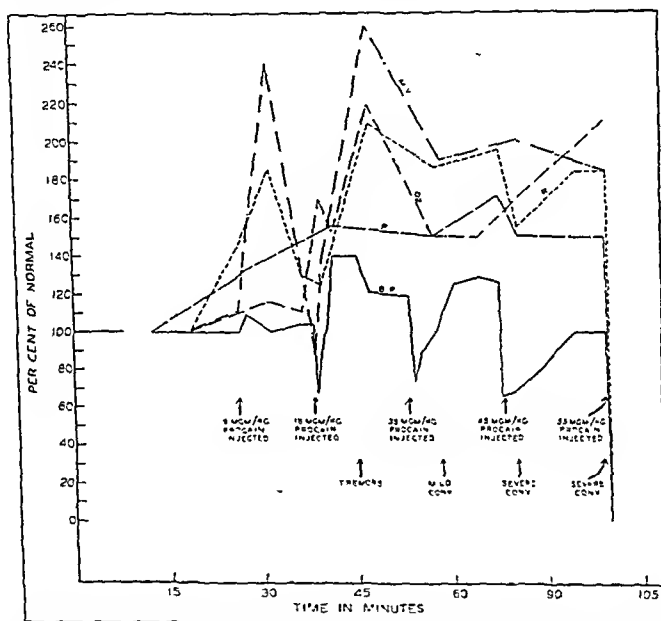


Fig. 3.—Chart showing changes in blood pressure, pulse, respiratory rate, minute volume, and oxygen consumption in a dog given gradually increasing intravenous doses of procaine.

zero occurs simultaneously with cessation of respirations. Except for the transient drop in pressure following injection of moderate doses of procaine, the blood pressure trend is much like that observed after subcutaneous injection of procaine. Pulse, respirations, minute volume, and oxygen consumption behaved much as in the preceding experiments.

From these observations one may say that the terminal circulatory collapse is not the result of any loss of plasma volume. It seems unlikely that death is consequent on any peripheral action of the drug. The abrupt and almost simultaneous cardiac and respiratory failure suggests rather that death ensues from central medullary paralysis, although this is not definitely proved.



Clinically two types of severe reaction to toxic doses of local anesthetics are observed. Briefly, in one, death is sudden and is characterized by abrupt circulatory collapse, and in some instances heart beat and respirations cease almost instantaneously. There may or may not be convulsions. The other reaction is more prolonged and is characterized by convulsive manifestations and finally respiratory and cardiac failure. The latter type has been often reproduced experimentally by subcutaneous injection of a fatal dose of procaine and the rapid death following intravenous administration of a lethal dose in experimental animals has been assumed to represent the collapse type of reaction.<sup>8, 9</sup> It has been suggested, therefore, that the one is dependent upon slow absorption of a toxic dose and the other upon rapid absorption of a toxic dose.

Although Hatcher and Eggleston<sup>10</sup> had found that heart beat and respirations ceased together after intravenous administration of novocaine in cats, Knoefel and his co-workers<sup>8</sup> suggested, from kymographic records of blood pressure and respirations following intravenous injections of cocaine in dogs, that death from intravenous injections is due to direct paralysis of the heart. It is interesting that the kymographic tracing which they have used to illustrate this point shows that respirations are stimulated immediately, even before the blood pressure has begun to fall, and that they cease altogether within forty-five seconds of the time the pressure has dropped to a critically low level, and within sixty seconds of the completion of the injection of cocaine. They felt that death after subcutaneous injections, on the other hand, was primarily a respiratory one. It has been generally assumed that the convulsive manifestations of these reactions are due to action of the drug on the brain and that respiratory failure is due to central medullary paralysis. In the early cocaine experiments of von Anrep<sup>11</sup> it was concluded that the changes in blood pressure were due to action of the drug on the vasomotor center, that the initial acceleration of the heart rate was due to the elevated blood pressure and to vagal paresis, and that death was due to respiratory failure.

My experiments confirm the general belief that the "collapse" type of reaction is more nearly reproduced by rapid absorption or by direct intravenous injection of procaine and the other type by slow absorption from subcutaneous or other tissues. As regards a different mechanism of death in the two instances, however, one would suppose a priori that regardless of the mode of injection or the site of lethal action, procaine must pass to this reactive center through the mechanism of the blood system and that there should be no essential difference in the type of death but only a difference in the duration of the reaction. It seems likely that after intravenous injection the heart should be paralyzed before the medullary centers and that after subcutaneous injection the centers should be poisoned before the heart.

My experiments suggest, though they do not prove conclusively, that in both the sudden and the more prolonged type of reaction, death occurs chiefly from central medullary paralysis. The sudden and brief reaction which follows intravenous injection of a lethal dose of procaine is exactly like the terminal phase of the more prolonged reaction following subcutaneous injection of a lethal dose. In both there is so constantly an almost simultaneous cessation of respiration and heart beat that it suggests that the mechanism is likely to be a central one affecting both cardiac and respiratory centers. As has been mentioned previously, after subcutaneous injection the heart usually but not invariably beats for a short time after respirations cease, and vice versa, after intravenous injection the heart often but not always stops a moment before the last respiration. Sometimes the heart beats after respiration ceases, and if the thorax is opened soon after respirations cease, the heart is always found to be beating feebly even though clinically it was thought to have stopped. Convulsions are constant after subcutaneous injections of a lethal or near lethal dose and almost constant after intravenous injections. Only when an overwhelmingly large dose has been given intravenously, when death is practically instantaneous, are convulsions apt to be absent, and even then there is ordinarily a general extensor thrust as the animal dies. After a small intravenous injection there is a temporary drop in blood pressure, very transient and followed by a rise to a higher than normal level. This observation suggests that procaine may stimulate output of adrenalin. When a low concentration of procaine is achieved by slow absorption, this fall in blood pressure is not observed. It has been noted that a very small intravenous injection of procaine causes no fall in blood pressure but an actual increase. It is possible that with slow continuous absorption into the blood stream of small amounts of procaine there is the initial rise, and that as the blood procaine level rises, through some physiologic adjustment the blood pressure continues normal or elevated. Only when a high enough concentration has been achieved to constitute a fatal level does the blood pressure fall precipitously, along with failure of heart and respiration. Apparently, levels of blood procaine concentration insufficient to cause the fatal collapse are sufficient to bring about stimulation of respiration, increase in pulse rate, alteration in the state of consciousness, and convulsions.

In order to see whether, regardless of the route of administration and the size of the dose required to cause death by the different routes, the animals die with roughly the same blood procaine levels, such determinations were made in a number of animals poisoned by procaine administered by different routes. Blood for assay was removed from the heart immediately after death. In Table I are summarized the results of this study and in Fig. 4 are illustrated the range in blood procaine levels according to the route and amount of procaine injected. It will

be seen that after intravenous, intrapleural, intramuscular, and subcutaneous injections, although the injected dose varied from 40 to 500 mg. per kilogram of body weight, the average unchanged procaine level was almost identically the same. Somewhat more variation occurred in the estimated total procaine levels, more of the acetylated procaine being present after subcutaneous injections. Following intraperitoneal injections the procaine levels at death were somewhat higher. Whether this observation means that much of the procaine was absorbed into the portal circulation and that perhaps some of that estimated as unchanged procaine was actually rendered innocuous during passage through the liver, I cannot say. It is possible that where procaine is freely passing

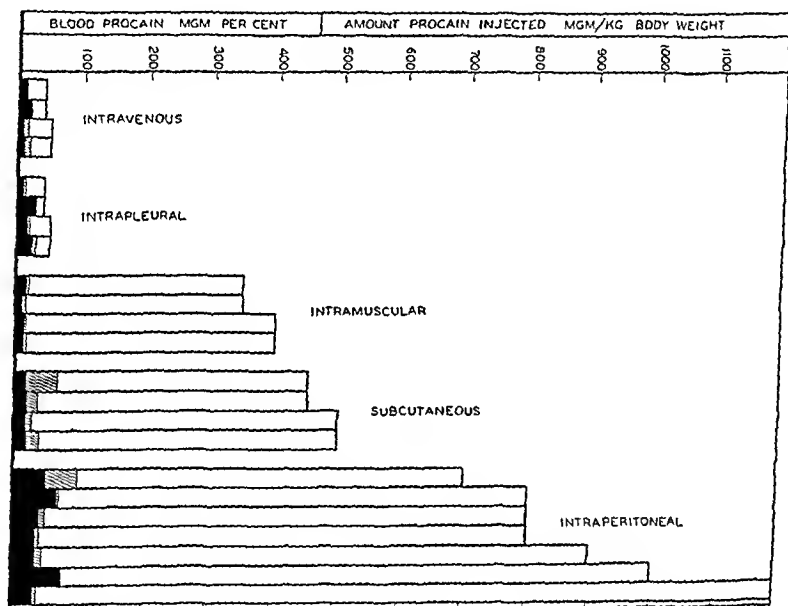


Fig. 4.—Chart showing blood procaine concentration at death according to the route and the amount of procaine injected in present free blood procaine concentration free and total procaine. The unshaded columns represent amount of body weight. Shaded columns represent; cross-hatched columns represent total; where there is no crosshatching the approximately equal.

into the blood system from such a large store, absorption may continue during the terminal period of antemortal collapse and thus raise the blood procaine level at death to a higher level than was actually present when the fatal reaction was induced. Altogether these studies seem to substantiate the idea that regardless of the route of administration, death depends upon the presence in the blood stream of a lethal concentration which is roughly the same regardless of its source.

It has been found repeatedly that the intravenous lethal dose of procaine and of other local anesthetics in experimental animals is considerably less than is the subcutaneous lethal dose. It seemed wise to

TABLE I

BLOOD PROCAINE LEVELS AT DEATH FOLLOWING ADMINISTRATION  
BY DIFFERENT ROUTES

ROUTE OF ADMINISTRATION	PROCAINE IN MG. PER KG. BODY WEIGHT INJECTED (AVERAGE)	FREE BLOOD PROCAINE IN MG. PER 100 C.C. (AVERAGE)	TOTAL BLOOD PROCAINE IN MG. PER 100 C.C. (AVERAGE)
Intravenous	45	11.5	14.4
Intrapleural	45	16.4	20.2
Intramuscular	375	11.0	15.6
Subcutaneous	475	15.7	40.7
Intraperitoneal	887	46.3	58.2

investigate in experimental animals the lethal dose of procaine administered by still other routes by which it might be deliberately or inadvertently injected into human patients. In Table II the data are summarized. Because the median lethal dose is much more accurate than an attempted estimate of the minimum lethal dose, results have been calculated in terms of the median lethal dose.<sup>12</sup> It will be seen that the intravenous median lethal dose is only one-tenth of the subcutaneous median lethal dose. Surprisingly enough, the intrapleural median lethal dose is almost as small as the intravenous, and it may be remarked that

TABLE II

SHOWING VARIATION IN MEDIAN LETHAL DOSE OF PROCAINE IN GUINEA PIGS  
ACCORDING TO ROUTE OF ADMINISTRATION AND ACCORDING TO  
AGE OF SUBJECT

ROUTE OF ADMINISTRATION	ALL ANIMALS*	YOUNG ANIMALS	OLD ANIMALS
Intravenous	41 (54)	41.5 (38)	38.5 (16)
Intrapleural	42 (25)	42 (15)	42 (10)
Paravertebral (thoracic)	115 (10)	115 (10)	
Paravertebral (lumbar)	250 (30)	280 (20)	213 (10)
Intramuscular	330 (25)	350 (15)	270 (10)
Subcutaneous	410 (56)	425 (47)	340 (9)
Intraperitoneal	750 (28)	765 (20)	725 (8)

\*The number in parenthesis indicates the number of animals used in each series.

death occurs almost as rapidly after an intrapleural injection as after an intravenous injection, and in just the same manner. Control intrapleural injection of similar quantities of normal salt solution produced no symptoms. When procaine is deposited in the thoracic paravertebral region, the median lethal dose is also remarkably small, being roughly one-fourth of the subcutaneous median lethal dose. In this series the accuracy of the injection was proved by autopsy inspection, the procaine having been colored with a dye. Animals in which the injection was either too superficial or partly intrapleural were excluded. The lumbar paravertebral median lethal dose is somewhat larger but still only a little more than one-half of the subcutaneous. The intramuscular median lethal dose is a little less than the subcutaneous. Again, surprisingly enough, the intraperitoneal median lethal dose is almost twice as large

as the subcutaneous. In general it may be said that the larger the median lethal dose, the longer the period of survival. Others have demonstrated that if procaine is *slowly* injected intravenously, the animal will survive considerably larger amounts than if it is administered with great rapidity.<sup>2</sup> This fact is undoubtedly due to the rapid destruction or detoxification of the procaine, which Hatcher and Eggleston believe takes place in the liver.<sup>2</sup> From this fact and from what I believe to be true as regards the fatal blood procaine level, I think the enormous differences which exist in the median lethal dose according to the route of administration are due to differences in the rate of absorption of procaine from the various tissues and body cavities. With the intraperitoneal injections another factor may possibly enter into consideration; namely, the absorption of some of the material into the portal circulation and its detoxification in the liver. Perhaps the presence of large lymphatic collecting trunks in the paravertebral region may contribute to the relatively rapid absorption from this area, and in the thoracic paravertebral region, diffusion through the pleura may be an added factor. The entire question of the rate of absorption of procaine and other substances from various body tissues will be the subject of a further report. Regardless of the mechanism, the importance of these observations in the clinical use of procaine is immediately apparent.

The statement has been made that procaine should be used in more guarded amounts in patients in poor physical condition than in those in vigorous health.<sup>4</sup> The question arises whether age is also a factor in the toxicity of procaine. Having on hand a number of guinea pigs about a year older than those ordinarily available, I thought it advisable to put this question to the test of experiment. The results are given in Table II. With the exception of the intravenous and intrapleural routes, the median lethal dose is somewhat smaller in the older group regardless of how the procaine is administered. The differences, however, are not great.

It is commonly believed that all local anesthetics should be used in the most dilute solutions that are satisfactory. In Table III are summarized the data concerning this point. It is seen that slightly larger

TABLE III

SHOWING EFFECT OF CONCENTRATION OF INJECTED PROCAINE SOLUTION UPON  
MEDIAN LETHAL DOSE IN GUINEA PIGS

ROUTE OF ADMINISTRATION	0.5% SOLUTION*	1% SOLUTION	10% SOLUTION
Intravenous	47 (16)	40 (8)	38 (30)
Subcutaneous		470 (16)	385 (10)

\*The number in parenthesis indicates the number of animals used in each group.

amounts of the more dilute solutions are tolerated. The differences are small and are, I believe, dependent upon the fact that the larger amounts of the more dilute solutions are necessarily injected more slowly in the

intravenous injections and are absorbed more slowly from the subcutaneous tissues than are the smaller amounts of the more concentrated solutions. Clinically, of course, a much more important consideration is this: ordinarily in infiltration anesthesia as large an amount of a concentrated solution will be required to obtain anesthesia as of a more dilute solution, and consequently the total amount of procaine used is apt to be much greater in the concentrated solution.

Since procaine is often used as a supplementary anesthesia during general anesthesia, I have studied the lethal properties of procaine given during ether anesthesia. Knoefel, Herwick, and Loevenhart<sup>8</sup> had observed in dogs that preliminary administration of morphine and rectal ether might reduce the symptoms of cocaine poisoning but was of no value in preventing death and that, indeed, with its use death might ensue with a sublethal dose. Tatum, Atkinson, and Collins<sup>13</sup> had previously found the inhalation of ether of no therapeutic value in cocaine poisoning. In my experiments the median lethal dose of procaine after ether anesthesia was determined in sixteen guinea pigs. The animals were kept asleep for five minutes with ether, the mask was removed, and varying amounts of procaine were injected intravenously. Under these circumstances, the median lethal dose was found to be only 15 mg. per kilogram of body weight in comparison with 41 mg. in the unanesthetized control animals. An effort was made to see whether the subcutaneous lethal dose was similarly reduced in animals kept asleep with ether, but was not entirely satisfactory. The procaine reaction itself is more prolonged with subcutaneous injections and is associated with loss of consciousness, so that it was difficult to estimate how much ether to give and one was never quite certain whether the animal was actually anesthetized with ether. The impression was that the lethal dose was somewhat less than in the unanesthetized animals.

The one prophylactic measure about which there is general agreement is the use of the barbiturate group of drugs. This measure was first introduced by Hofvendahl<sup>14</sup> and has been supported by Tatum, Atkinson, and Collins,<sup>13</sup> and others. Downs and Eddy<sup>15</sup> thought that barbital increased the fatal dose of cocaine in rats by about 10 per cent. Knoefel and his co-workers<sup>8</sup> found that sodium barbital and paraldehyde increased the minimum subcutaneous lethal dose of cocaine in the rabbit from 100 to 150 mg. per kilogram and in the dog from 26 to 100 mg. per kilogram, and that monkeys which died from 30 mg. per kilogram survived as much as 100 mg. per kilogram if barbital and paraldehyde were given beforehand.

Since I had obtained data concerning the reduction of the subcutaneous median lethal dose in guinea pigs if the procaine was introduced by other routes, I thought it important to see just how much the median lethal dose could be increased through the prophylactic use of

one of the barbiturates. Maloney<sup>9</sup> has shown that the most effective barbiturates are those of high toxicity such as nembutal, dial, and pernoeton. In these experiments nembutal was used, each animal being given 0.8 e.e. per kilogram of body weight of a 4.2 per cent solution intraperitoneally twenty minutes before administration of the procaine. The animals were sound asleep, almost completely anesthetized. The dose was safe as determined with a number of control animals. The results are summarized in Table IV. The intravenous and the intrapleural median lethal doses were not increased but were actually decreased somewhat; the intramuscular and subcutaneous median lethal doses were increased by about 70 per cent.

TABLE IV  
SHOWING PROPHYLACTIC EFFECT OF NEMBUTAL ON MEDIAN LETHAL DOSE  
OF PROCAINE IN GUINEA PIGS

ROUTE OF ADMINISTRATION OF PROCAINE	NEMBUTAL GIVEN BEFORE PROCAINE*	UNTREATED CONTROLS
Intravenous	35 (10)	41.5 (38)
Intrapleural	35 (12)	42 (15)
Intramuscular	610 (16)	350 (15)
Subcutaneous	700 (16)	425 (47)

\*The numbers in parenthesis indicate the number of animals used in each group.

Although the barbiturates are of some aid in the prophylaxis and treatment of local anesthetic overdosage when absorption is slow, they are of no aid in preventing or treating the reactions which follow rapid absorption of a toxic dose. No very satisfactory treatment for such reactions has been demonstrated. In ten guinea pigs given 50 mg. per kilograms of procaine intravenously, 0.05 e.e. of eoramine given intravenously immediately thereafter did not save a single animal. Five-hundredths cubic centimeter of eoramine was determined on control animals to be a safe dose; 0.08 e.e. caused convulsions. Similarly, ten guinea pigs given 50 mg. per kilogram of procaine intravenously could not be saved by the intravenous injection immediately thereafter of 0.025 e.e. of metrazol, although the heart beat and respirations continued perhaps a moment or so longer than usual. Even when the metrazol was mixed with the procaine before injection, none of the animals survived. Artificial respiration in these animals did not prevent death. The amount of metrazol used was found by injections into control animals to be a safe dose.

#### DISCUSSION AND SUMMARY

It appears likely from the data presented as well as from certain material in the literature that all or nearly all of the symptoms arising from an overdose of procaine are due to affection of the nervous system and chiefly to affection of the central nervous system. Death is probably due essentially to medullary respiratory and cardiac paralysis.

There is no significant reduction in plasma volume during procaine reactions. The essential difference between the types of reaction that follow rapid absorption or direct intravenous injection of procaine on the one hand, and slow absorption from the subcutaneous or other tissues on the other, seems to be the duration of the reaction. The terminal failure of vital functions appears to be the same in both types. Death seems to be contingent upon a certain critical concentration of procaine in the blood, varying somewhat in individuals, but in general being of roughly the same order.

The lethal dose of procaine varies widely according to the route of administration. The intravenous median lethal dose is only one-tenth as great as the subcutaneous, and the intrapleural median lethal dose about the same. The thoracic paravertebral median lethal dose is little more than one-fourth as large as the subcutaneous, and the lumbar paravertebral about one-half as large. The intramuscular median lethal dose is somewhat smaller than the subcutaneous, and the intraperitoneal almost twice as large. These enormous differences in toxicity of procaine with different routes of administration are probably due to differences in the rate of absorption of the drug. It is obvious from these data that one should be very careful not to inject procaine intravenously or intrapleurally. In paravertebral injections, especially in the thoracic region, only small amounts of procaine should be used. One need not be concerned about the injection of moderate amounts of procaine into the peritoneal cavity.

A given amount of procaine is somewhat more toxic if administered in a concentrated solution than in a dilute solution, probably because of the more rapid absorption of the former. A more practically important reason for using only dilute solutions is the fact that satisfactory anesthesia can frequently be obtained with an actually smaller amount of procaine if a dilute solution is used. Anything that slows the absorption of procaine makes it safer. Others<sup>2</sup> have demonstrated that adrenalin mixed with procaine brings about an increase in tolerance to the drug through slowing the rate of absorption.

The old appear to tolerate procaine somewhat less well than the young. Other conditions which seem to decrease tolerance are severe hemorrhage<sup>2</sup> and probably damage to the liver, since procaine is thought to be largely detoxified in this organ.<sup>2</sup> Ether anesthesia definitely decreases the lethal dose of procaine given intravenously and probably also if given by other routes.

As regards prophylactic and therapeutic measures the experimental literature is full of contradictions. Salent and Nadler<sup>17</sup> thought alkalies given intravenously before cocaine increased the tolerance to the drugs in cats, and Knoefel and co-workers<sup>8</sup> found them of no value in cocaine poisoning by intravenous injection in dogs and rabbits, nor did Eggleston and Hatcher<sup>2</sup> find them of any value in saving cats after intravenous



injections of various local anesthetics. Eggleston and Hatcher<sup>2</sup> found that caffeine had no prophylactic influence on the toxicity of intravenously injected local anesthetics, but Nielsen and Higgins<sup>18</sup> found it of a little value in counteracting the effects of subcutaneously administered butyn. Dragstedt and Lang<sup>19</sup> thought atropine of some prophylactic value, but Knoefel and his co-workers<sup>8</sup> found that it did not influence the outcome in cocaine poisoning in rabbits following subcutaneous injections, nor did Eggleston and Hatcher<sup>2</sup> find it of value in intravenous injections of various local anesthetics in cats. Knoefel and associates<sup>8</sup> found ephedrine of no prophylactic value and Nielsen and Higgins<sup>18</sup> found it of questionable value. Eggleston and Hatcher<sup>2</sup> thought adrenalin combined with artificial respiration of definite therapeutic value in cats poisoned with cocaine injected intravenously. Nielsen and Higgins<sup>18</sup> thought pituitary solution of prophylactic and therapeutic value in rabbits and dogs poisoned with butyn given subcutaneously, but Knoefel and his co-workers<sup>8</sup> thought it of no value in cocaine poisoning in cats and dogs. Eggleston and Hatcher<sup>2</sup> thought ouabain of prophylactic value before intravenous injections of various local anesthetics in cats, but Knoefel and his co-workers<sup>8</sup> found it did not help with intravenous injection of cocaine in a few dogs and cats. Hyoscine, morphine, morphine and rectal ether, chloral hydrate, potassium cyanide, amyl nitrite, intravenous saline solution, and calcium appear to be without value.<sup>2, 8, 10, 18</sup> Tatum and Collins<sup>16</sup> found artificial respiration efficacious in treating rabbits injected subcutaneously with cocaine, but not dogs. With cats given toxic doses of various local anesthetics intravenously, Eggleston and Hatcher<sup>2</sup> found artificial respiration alone or combined with cardiac massage of no aid, but of value combined with the intravenous administration of adrenalin.

The outstanding observation about which there is general agreement is that the barbiturates seem to be of value prophylactically and therapeutically against subcutaneously administered local anesthetic agents.<sup>8, 9, 13-16</sup> The higher the animal as regards brain development, the more effective the barbiturates seem to be. The ideal barbiturate is apparently one combining high toxicity and long-continued action.<sup>9</sup> Tatum, Atkinson, and Collins<sup>13</sup> are of the opinion that the deleterious effect of the local anesthetic on the respiratory center is by way of the cerebrum and that essentially a tetany of the respiratory center with ultimate exhaustion occurs. They feel that the barbiturates are effective through depressing the higher functions of the brain as well as the respiratory center. Whether this is the correct explanation I cannot say. Nor can I explain why only the barbiturates are effective and apparently no other central nervous system depressants, sedatives, and hypnotics; for example, morphine, ether, chloral hydrate, etc. Nor can I explain why the barbiturates are effective against local anesthetics

slowly absorbed, but not when rapidly absorbed; that, indeed, in the latter case tolerance may be decreased. The explanation of Knoefel and his co-workers<sup>8</sup> that this is due to the direct action of the anesthetic on the heart does not seem entirely satisfactory.

In the present study it was found that nembutal given before procaine increased tolerance about 70 per cent when the procaine was given subcutaneously or intramuscularly, but decreased tolerance slightly when the procaine was given intravenously or intrapleurally.

I was unable to save animals given procaine intravenously by the intravenous administration of coramine or metrazol.

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# REACTIONS TO LOCAL ANESTHETIC AGENTS

## II. A CLINICAL REPORT

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COCAINE was first used as an agent for inducing local anesthesia following the discovery of its anesthetic properties by von Anrep<sup>1</sup> in 1880 and its applicability in ophthalmological surgery through the experimental and clinical observations of Koller.<sup>2</sup> Hardly had its use been well established in surgical practice before the necessity for substitutes arose because of the habit-forming property of this drug and especially because of the too common reactions which followed its use. These reactions were frequently mild in character and recovery ensued, but too often they were severe and even fatal.

A dozen or more substitutes were introduced, all alike in some respects and each with certain virtues and defects. They are all, like cocaine, lipid soluble alkaloids. None is habit forming. They vary in effectiveness when topically applied to mucous membranes, in the duration of anesthesia, and in other respects. It is not within the province of this report, however, to discuss the relative merits or the special field of application of each of these anesthetic agents. Suffice it to say, first, that for nerve blocking and local infiltration there is general agreement that procaine is reliable, effective, and the safest of all these agents; and second, that cocaine and the entire group of cocaine-like anesthetics are similar in the types of reaction which they may evoke, although they differ in the frequency with which their use is attended by such an untoward effect.<sup>3-7</sup>

It is my purpose to discuss these reactions in regard to their character, prevention, and treatment and to describe some illustrative cases which have occurred in the Johns Hopkins Hospital. I shall limit myself to reactions following the use of these agents in topical application, local infiltration, and nerve blocking. I shall not consider the reactions which occasionally follow spinal anesthesia since there is good evidence that they are ordinarily to be ascribed to the anesthesia obtained rather than to idiosyncrasy or to overdosage of the drug. For like reason I shall exclude reactions following caudal anesthesia. In one recent fatal case in the Johns Hopkins Hospital the anesthetic had been inadvertently injected into the subarachnoid space, as was proved by analysis of the cerebrospinal fluid.

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About twenty years ago the American Medical Association's Committee for the Study of Toxic Effects of Local Anesthetics asked that all reactions be reported to it, and in 1924 and again in 1928 Mayer published the fatal cases which had been submitted.<sup>5, 6</sup> Among other recommendations the request was made that all severe and fatal reactions be recorded in the literature. Few such cases have been reported. Whether this is indicative of the extreme infrequency of these reactions or to a failure to report them, I do not know. If the latter is the case, we may be lulled into a false sense of security. To call them to the attention of the medical profession need cause no undue alarm nor undermine the correct general impression as to the relative safety of local anesthesia, and yet may keep us alive to the possibility of their occurrence, and make us more alert in utilizing the known safeguards in an effort to prevent them and better prepared to treat them once they occur. Furthermore, discussion may stimulate experimentation which may lead to better prophylaxis and treatment. It is with these ideas in mind that I submit this report.

The reactions may be divided into two types; first, those presumably dependent upon true hypersensitivity of the patient to the drug; and second, those resulting from absorption of a toxic dose. The following are examples of the first type of reaction.

CASE 1.—A minute amount of novocaine was injected into the skin of a patient preparatory to a lumbar puncture.\* The injection had hardly been made before the patient began to wheeze in a typical asthmatic attack. She immediately asked the physician whether he had not injected novocaine, telling him that her only other attack of asthma had followed injection of this drug. She did not have hay fever or allergy to any of the common antigens. Before epinephrine could be secured and administered the brief but momentarily alarming attack had subsided.

MacKay<sup>7</sup> reported a somewhat similar reaction in a tuberculous patient who had wheezing, labored breathing, feeling of tightness in the mediastinum, weak and rapid pulse, and prostration after each pneumothorax refill done with local novocaine infiltration: She had had some wheezing before, independent of the refills, and this continued, but had no reactions following her refills when they were carried out without anesthesia.

CASE 2.—(Unit No. 124977.) The patient, a 25-year-old medical student, had incision of two small chalazions on the lower lid and a small hordeolum on the upper lid of the right eye after instillation with 1 per cent pontocaine solution. Two days later he had extreme swelling and injection of the conjunctivae of the right eye. The following day the chemosis and conjunctival injection were very great and the face was puffy about the outer canthus. There was little discharge, and smear and culture were negative. He was admitted to the hospital but the frequent use of argyrol and boric acid followed by irrigations of zinc sulfate brought about no

\*Cited to me by Dr. Paul Padgett of the Department of Medicine, Johns Hopkins University.

improvement. In fact, the reaction proceeded to a point where there was actually some loss of substance. Pontocaine reaction was finally suspected, and eight days after the operation a skin sensitivity test was carried out, 0.1 c.c. of 1 per cent procaine being injected intradermally into one arm and the same amount of 0.5 per cent pontocaine into the other. He had no reaction to the procaine, but a violent reaction to the pontocaine. In twenty-four hours the area of reaction measured 6 by 10 cm. and there was some necrosis in the central portion. Both the ocular and the cutaneous reaction subsided slowly, and he was discharged seventeen days after the operation.\*

A case similar to this one has been reported by Pfeiffer,<sup>10</sup> and the same general sort of reaction has been encountered by others. One of MacKay's<sup>9</sup> tuberculous patients had pain locally after each pneumothorax refill with novocaine anesthesia and remained entirely free of this local soreness when these treatments were carried out without anesthesia. Mullen<sup>11</sup> recorded two similar cases of local pain, tenderness, erythema, and induration after each refill, with complete absence of such reaction when the refills were done without novocaine. A skin test in the arm with 0.1 c.c. of novocaine in each case resulted in a typical local reaction.

It seems entirely likely that reactions of these sorts represent a true hypersensitivity to the drug. I know of no experimental production of these reactions. Epinephrine or ephedrine should be of some aid in treating them.

The reactions which are ascribed to a toxic dose may be mild or severe. In the mild reactions there may be restlessness, palpitations, perspiration, pallor, loquacity, nausea, and tremor. There is good evidence that the incidence of such reactions may be substantially reduced by preliminary medication with one of the barbiturates and that the reactions may likewise be successfully treated with barbiturates.<sup>12-15</sup> The severer reactions are generally divided into two groups, one characterized by convulsions and respiratory failure, the other by sudden collapse. In the former there may be apprehension, excitement, delirium, and dyspnea. There are always convulsions, and death is ordinarily said to be respiratory in type. The second group is associated with sudden pallor, tachycardia, fainting, and shock. Cardiac and respiratory failure occurs very rapidly. I am not entirely certain that death in the first type is primarily due to respiratory and in the second to cardiac failure,<sup>16</sup> as is commonly believed. The barbiturates are apparently effective prophylactically and therapeutically in the first type of reaction, but of no value in the second.<sup>13-18</sup>

These reactions are exemplified by the following cases which have occurred in the Johns Hopkins Hospital. One death occurred with cocaine, two with butyn and cocaine, and one with procaine. Three additional nonfatal procaine reactions are included.

\*This case is reported through the courtesy of Dr. J. M. McLean.

CASE 3.—(Unit No. F 52324.) The patient, a colored male, 32 years of age, came to the Rectal Clinic in 1916 complaining of bleeding hemorrhoids. Nothing else of consequence was found in the history or on physical examination. He returned a few days later for hemorrhoidectomy under local quinine-urea anesthesia. With the patient in the knee-chest position, the area was properly prepared and local infiltration was carried out, 25 c.c. of the anesthetic solution being used. The injection was hardly completed when the patient suddenly cried out in an incoherent manner, fell forward on his face, and began frothing at the mouth. He rapidly lost consciousness and had several violent clonic and tonic convulsions. In spite of attempts at artificial respiration it was impossible to restore pulse or respirations, which had rapidly disappeared; the patient did not regain consciousness and died within about five minutes. On analysis of the anesthetic solution it was found that by mistake the operator had been given 10 per cent cocaine.

CASE 4.—(Unit No. J 76779.) The patient was a white male, 72 years of age, who came to the Nose and Throat Dispensary in 1931 because of hoarseness of six months' duration. He was found to have a carcinoma of the larynx. After a preliminary spray with 5 per cent butyn, cocaineization of the larynx with a 20 per cent solution was begun in preparation for biopsy. During this procedure he began to complain of being short of breath, and quickly stopped breathing. A tracheotomy and artificial respiration were of no avail. A note records that the heart continued to beat at least five minutes after respirations ceased.

CASE 5.—(Unit No. 175032.) The patient, a 43-year-old male, was admitted to the hospital in June, 1939, with a carcinoma of the lung for which a total pneumonectomy on the right side was performed. An empyema associated with a bronchial fistula developed and was treated by drainage with an intercostal catheter and bronchoscopic applications of silver nitrate. He was discharged in September, and returned in October and again in November for bronchoscopy. On the latter occasion his larynx was cocaineized with application of 20 per cent cocaine after a preliminary spray with 5 per cent butyn. As soon as this preparation had been completed and he was placed on the bronchoscopic table, he complained of shortness of breath and suddenly had a generalized convulsion. The mouth was quickly forced open and the bronchoscope passed, through which oxygen was delivered. He rapidly lost consciousness, the convulsive seizure persisted, and after about twenty minutes respirations ceased. Although the clinical note makes no mention of it, one of those present thinks that adrenalin was given intravenously. The patient had been similarly cocaineized for four previous bronchoscopic treatments without reaction.

CASE 6.—(Unit No. 196469.) A white female, 50 years of age, who had had an arthrodesis on the left hip for traumatic arthritis, was readmitted in July, 1940, about five weeks after discharge, because of pain in the leg and thigh, which was still in a recently applied spica cast. It was thought that she had a thrombophlebitis, and a paravertebral sympathetic block with 2 per cent procaine was carried out. Almost immediately she had a severe reaction characterized by pallor, rapid pulse, and faintness. She was given 2 c.c. of metrazol intravenously and prompt recovery ensued.

CASE 7.—(Unit No. 206971.) A 52-year-old white male was admitted in August, 1940, with femoral thrombophlebitis. A lumbar paravertebral sympathetic block was carried out with 2 per cent procaine. About 4 c.c. each was injected at the level of the first, second, and third lumbar ganglia. The total amount used is not stated, but was thought by the operator to have been 20 or 30 c.c. Five or ten minutes after the injection the patient felt faint and nauseated, the pulse became

rapid and thready, and blood pressure fell to about 50 systolic. He was given 0.5 c.c. of caffeine sodium benzoate intramuscularly and 4 c.c. of coramine intravenously. His symptoms and the signs of shock persisted for almost two hours. Recovery followed.

CASE 8.—(Unit No. 169098.) The patient, a 7-year-old colored girl, came to the Accident Room in September, 1940, with a Y-shaped laceration of the right arm which she had sustained in a fall. Some of the fibers of the triceps muscle had been divided. The surrounding area was prepared with kalmamid and infiltrated with about 15 c.c. of 2 per cent procaine, after which the wound itself was cleaned with surgical detergent and kalmamid. Some bleeding started, a tourniquet was applied, and repair was begun. After the muscle was approximated and suture of the skin was begun, the patient suddenly became apneic and respirations ceased. She could not be roused, and the pulse was very rapid though it felt of normal volume. Artificial respiration was begun. After about two minutes she began to gasp for air in short respiratory excursions. Respirations became normal after a few minutes though she did not respond for several minutes more. About ten minutes after the reaction began she appeared normal.

CASE 9.—(Unit No. 208659.) A 40-year-old white female was admitted in August, 1940, because of Raynaud's disease and scleroderma. The following day skin temperature studies and a dorsal procaine block were done. Six cubic centimeters of 2 per cent procaine was used in infiltrating the skin and the subcutaneous and intramuscular tissues. The needle was introduced paravertebrally about fifteen minutes after the injection was begun. Ten cubic centimeters of procaine was now injected, 2 c.c. at a time. Almost immediately the patient said she felt a little faint, and she was allowed to lie down. She said she still felt faint. The pulse seemed of normal volume and was not increased in rate. Suddenly, five minutes after the injection, she lost consciousness, the pulse disappeared, and heart and respirations ceased, all about simultaneously. The foot of the bed was quickly elevated, and coramine, caffeine, and adrenalin were given intravenously in rapid succession. Artificial respiration was begun with oxygen inhalation. Coramine was again given intravenously, and when no response was obtained, 4 c.c. was injected into the heart. An artificial respirator delivering oxygen was by now in use. Suddenly, fourteen minutes after the collapse occurred, she began to breathe spontaneously, the radial pulse became perceptible, and the heart sounds were fairly vigorous. Her face, however, remained cyanotic. After five minutes, heart and respirations ceased as suddenly as they had reappeared. During the last few minutes there was a little frothing at the mouth. During the reaction she had had several hundred cubic centimeters of 5 per cent glucose and normal saline solution intravenously. At the end coramine was again injected into the heart, but without effect.

Since the few centimeters of procaine remaining in the flask had been spilled during the procedure, none remained for testing. The batch of procaine solution of which this was a sample, however, caused no other reactions. The injection was carried out with a 2 c.c. syringe. Each time the syringe was removed for refilling no blood and no spinal fluid was seen at the open end, and there was no sucking in of air. Each injection was preceded by attempted aspiration; no blood, spinal fluid, nor air was withdrawn. During the five minutes when the patient was breathing there was ample evidence that no high spinal anesthesia had been obtained. This fact is mentioned because in an attempted sympathetic block it is possible to inject the fluid into the subarachnoid space. As White has pointed out,<sup>10</sup> this accident is more likely to happen if the needle is directed cephalad, but this was not the case in this instance. In neither this nor the other two cases was there any evidence that a subarachnoid, intravenous, intrapleural, or intraperitoneal injection had been made, and the usual care had been exercised to guard against these possibilities. In neither this nor the other cases was adrenalin used with the procaine.

It will be noted that one of the cocaine and all of the procaine reactions occurred within the past year. I am unable to find in the hospital records other cases of severe or fatal reactions to local anesthetics. This fact does not necessarily mean that none has occurred. Unfortunately, because of possible failure to include these diagnoses in the index files, any that may have occurred cannot be traced. Undoubtedly other nonfatal reactions have occurred. If other fatal reactions have escaped detection, they must be few in number.

It is extremely unfortunate that in none of the fatal cases was autopsy permission obtained, although it is true that in autopsies on other patients who died apparently of such reactions, nothing significant has been observed. Hatcher and Eggleston<sup>20</sup> have suggested that in cases where small amounts of novocaine have been used, death may possibly be due to some abnormality of the heart or respiratory center whereby susceptibility to the toxic action of the drug is increased to an extraordinary degree. Follis<sup>21</sup> has recently reported cases which suggest that sudden death during general anesthesia may be at least partly dependent upon some anomaly of the coronary vessels. It is equally unfortunate that blood was not drawn at death for determination of blood procaine concentration, as such studies might throw some interesting light upon the subject.<sup>16</sup>

In connection with this general problem of reaction, certain questions naturally arise. In the first place, one would like to know what constitutes the essential difference between the so-called "convulsive-respiratory failure" and "collapse" types of reaction. In my experiments<sup>16</sup> the sudden deaths where the procaine was injected directly into the blood or was absorbed with great rapidity more nearly resembled those clinical reactions designated as the collapse type, and the more prolonged reactions resulting from injection of a fatal dose subcutaneously or by some other route where absorption is slow were more like those clinical reactions designated as the convulsive type. Except for the time interval before the onset of the reaction and for the duration of the reaction, no essential difference was noted. Even where the reaction was prolonged the terminal phase resembled remarkably the briefer reactions. The work suggested, though the point could not be definitely proved, that in all instances death was primarily due to central medullary cardiac and respiratory paralysis. In all the experimental reactions convulsions were the rule. Clinically, the collapse type of reaction is said to be characterized by circulatory failure and death from cardiac failure. This is certainly not always true. In Case 4 there was a sudden collapse and rapid death, associated with no convulsions, and yet the heart continued to beat after respirations ceased; and in Case 9, where the initial symptom was a feeling of faintness, heart and respirations ceased simultaneously, began again simultaneously during the brief



period of resuscitation, and again ceased at the same instant.\* It is said that the collapse type of reaction is either accompanied by no convulsions at all or by a single convulsion. In Case 3, where sudden collapse occurred and death took place within the short space of five minutes, there were vigorous convulsions up to the end. As a matter of fact, one would have difficulty in fitting a number of the cases I have reported into either the one category or the other according to the usual descriptions. One must suspect that in human beings, as in laboratory animals, the important factor is the rate of absorption and the amount of the anesthetic absorbed, and that upon these factors depend the duration and the character of the reaction.

Second, one would like to know what constitutes a "safe" dose. This question it is impossible to answer. Liebel<sup>22</sup> injected into himself 400 mg. of 1 per cent novocaine and an hour later 750 mg., without ill effect. Braun<sup>23</sup> used clinically as much as 1,500 mg. of procaine in 0.5 or 1 per cent solution, without reaction. Siegel<sup>24</sup> used 3,000 mg. of 0.5 per cent novocaine, without reaction. Bieter<sup>7</sup> suggested 430 mg. as a safe dose and one-half as much in highly vascular areas. Labat,<sup>6</sup> who had a vast experience, gives as a maximal safe dose 2,500 mg. of 0.5 per cent novocaine, 1,500 mg. of 1 per cent, and 1,200 mg. of 2 per cent. These estimates are chiefly on a basis of clinical experience. The death from procaine poisoning which I have reported occurred following the use of 320 mg. As little as 30, 20, and even 12.5 mg. have resulted in fatalities.<sup>5, 20</sup> It is apparent that the "safe" dose is unknown and that what is a safe dose in the majority of cases may in a rare instance prove fatal. In addition to route of administration and rapidity of absorption, which influence the toxicity and which I shall discuss later, it is clear that in certain fatalities a true idiosyncrasy must occasionally be taken into consideration.

Another question concerns the concentration of the anesthetic solution. The general belief is that one should use as dilute a solution as is satisfactory. Mayer<sup>8</sup> felt that procaine should be given in no greater concentration than 1 per cent; Labat,<sup>6</sup> Bieter,<sup>7</sup> and others, in no more than 2 per cent. Labat<sup>6</sup> suggested that the actual amount of novocaine which constitutes a safe maximal dose may be twice as much in 0.5 as in 2 per cent solution. Experimental animals tolerate slightly larger amounts of procaine if it is given in dilute solution, probably because the larger amounts of the more dilute solutions are absorbed more slowly.<sup>16</sup> It is well known that much more than an ordinary intravenous lethal dose may be injected without causing death if the solution is injected slowly.<sup>24</sup> There are other valid reasons why dilute solutions should be used. Anesthesia is likely to be obtained with an actually smaller amount of the

\*In the procaine reactions which were not fatal, two (Cases 6 and 7), were characterized by circulatory collapse, but one (Case 8) was characterized primarily by sudden cessation of respiration and loss of consciousness.

anesthetic if a dilute solution is employed for the reason that in ordinary infiltration a certain volume is almost sure to be necessary to obtain satisfactory anesthesia regardless of its concentration; also, if some of it were to be inadvertently injected into the blood stream, it would be much less apt to prove fatal if a dilute solution were being used. Likewise, except where specifically contraindicated, adrenalin should always be mixed with the anesthetic solution because this combination both slows the rate of absorption and increases the duration of the anesthesia.<sup>25</sup> The sole advantage of using a more concentrated solution seems to be that the duration of anesthesia may be longer if the concentration is greater.

Still another question concerns the route of administration. It is striking that all three of the procaine reactions which I have reported followed paravertebral sympathetic block. I know of no other reported fatalities with this sort of injection. The technique used was that recommended by White<sup>26</sup> for dorsal and by Ochsner and DeBakey<sup>27</sup> for lumbar block, except that these authors used 1 per cent solution; whereas, in these cases 2 per cent was used. The actual amount of procaine given in the fatal case, however, was well within the limits of what is ordinarily considered a safe dose. As has been mentioned before, the usual precautions were observed to avoid inadvertent injection into the blood stream, subarachnoid fluid, peritoneum, or pleura. It has long been known that experimentally the intravenous lethal dose is much less than the subcutaneous. My experiments<sup>16</sup> with guinea pigs have revealed what I believe to be clinically important; namely, that the median lethal dose of procaine is only one-tenth of the subcutaneous if the solution is given either intravenously or intrapleurally, one-fourth if given in the thoracic paravertebral region, one-half in the lumbar paravertebral area, and about eight-tenths if given intramuscularly. If given intraperitoneally, however, the median lethal dose is about twice as large as the subcutaneous. It is believed that these differences are due to differences in the rates of absorption from the various tissues and body cavities. Obviously, then, one should use smaller amounts of anesthetic solutions in those tissues where the lethal dose is known to be small.

Certain other factors probably reduce the lethal dose somewhat. The old tolerate procaine slightly less well than the young.<sup>16</sup> Acute hemorrhage, circulatory depression, decrease in liver function, and other conditions which might interfere with the proper delivery of the procaine to the liver for detoxification or which might interfere with this process in the liver itself, probably decrease tolerance to procaine and the other anesthetic agents.<sup>25</sup> Ether anesthesia also probably decreases tolerance to procaine;<sup>16</sup> hence, one should be somewhat guarded in the amount used in supplementing general anesthesia.

Finally, another important question is how the reactions may be prevented and treated. The one agent which has been generally found of

value is the group of barbiturates. Experimentally, deep hypnosis approaching surgical anesthesia induced with one of the barbiturates definitely increases tolerance to the local anesthetics in a variety of animal species, provided the anesthetic is administered by a route where slow absorption takes place.<sup>16</sup> It appears that clinically moderate doses of the barbiturates are effectual in preventing the milder type of toxic reaction and the severer sort characterized by convulsive manifestations and rather prolonged duration. In experimental work the barbiturates are entirely ineffective in preventing reactions of the type which follow rapid absorption of the anesthetic; presumably also those clinical reactions which come on rapidly and terminate quickly and which are apparently the result of rapid absorption of a toxic dose, cannot be prevented by barbiturates. Those reactions, the incidence of which can apparently be reduced by preliminary administration of barbiturates, can sometimes be effectively treated by the intravenous administration of one of the barbiturates once the reaction has begun. It appears that the ideal barbiturate is one of high toxicity and long continued action.<sup>17</sup> Nembutal, dial, and pernocton have been demonstrated to be effectual. Seconal might prove valuable in prophylaxis, and sodium pentothal might be a useful agent in the treatment of these reactions. The reactions which follow rapid absorption are more difficult to treat. Experimentally, one investigator has found intravenous adrenalin and artificial respiration of value.<sup>25</sup> Pituitary solution has been reported to be effective in experimental reactions,<sup>28</sup> but others have found it disappointing.<sup>29</sup> In some of the clinical cases I have reported eoramine and metrazol may have been of aid, although experimentally I could not demonstrate their efficacy.<sup>16</sup> Since preliminary administration of the barbiturates is not only ineffective in preventing reactions which follow rapid absorption of the anesthetic agent but may actually decrease the lethal dose of the agent,<sup>16</sup> it is all the more mandatory that every care be exercised to prevent injection into the blood stream or into tissues from which rapid absorption takes place.

From these considerations and others one might make certain suggestions, many of which have been emphasized by other workers.

1. Cocaine should never be given by injection. Urethral instillation of an anesthetic should not be made in the presence of trauma. Procaine is probably the most satisfactory anesthetic for infiltration or nerve blocking.

2. All anesthetics should be used in as dilute solution as is satisfactory; procaine should probably not be used in concentration greater than 1 per cent. Except where specifically contraindicated, adrenalin should always be used in the anesthetic solution. Injections should be made slowly and with care to avoid injection into the blood stream; an anesthetic should not be injected directly into the pleural cavity; and extreme care should be exercised as to the quantity of the anesthetic used

in paravertebral injections. It should be kept in mind that the fatal dose may be less in elderly and very ill patients and those with poor circulation and reduced liver function. Large amounts of local anesthetics should not be used in supplementing general anesthesia. All solutions should be properly labeled so that no mistake can be made as to what is being injected.

3. One of the barbiturates should be used as preliminary medication. If a reaction occurs which seems predominantly convulsive in character, and particularly if its onset suggests relatively slow absorption of the anesthetic, an intravenous injection of one of the barbiturates should be made. Until something more specifically helpful is learned, those reactions which come on rapidly and are associated with early collapse should probably be treated with intravenous injection of adrenalin and of one of the cardiorespiratory stimulants such as eoramine or metrazol. If the pulse has disappeared, the injection should be made into the heart. If the respirations are compromised, artificial respiration and oxygen inhalation should be begun immediately. If a severe or fatal reaction occurs, an analysis of the anesthetic concentration in the blood should be carried out.

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# THE MOBILIZATION AND DEPOSITION OF BONE CALCIUM BY ELECTROLYSIS

## A PRELIMINARY REPORT

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THE effect of electrolysis on bone has not been reported in recent medical literature. The following observations indicate that electrolytic action can modify tissue response about an electrode in contact with bone.

Two platinum bands were wrapped subperiosteally around the femur of an anesthetized rabbit. The bands were 2 mm. wide and were applied snugly to the cortex about 1 cm. apart. Their free ends were insulated



Fig. 1.—Femur illustrates mobilization of calcium from cortex underlying the positive electrode with deposition of calcium about the electrode. Ulna and radius show mobilization of calcium post mortem without redeposition.

with rubber and left projecting from the wound. During the fifth to eighth postoperative days a 1½ volt battery was connected to the bands for a total of about twenty-four hours. The rabbit was then sacrificed.

Examination of the excised femur revealed a shell of calcium-containing material bridging the positive electrode. The cortical bone at either end of this shell was roughened by adherent granular masses similar to

early calcium deposition in callous about a fracture. When the positive platinum band was removed, parallel troughs 1.5 mm. wide were noted encircling the bone. These depressions corresponded roughly to the edge of the band. The cortex beneath the electrode was furrowed and rough. There was no gross reaction about the negative electrode.

Roentgenologic examination revealed transverse bands of decreased density underlying the region once occupied by the positive electrode. When seen tangentially, these bands appeared as distinct depressions in the cortex. A bridge of opaque material spanned the area described.

Control experiments showed that the electrodes themselves did not produce the changes described. The passage of current through electrodes applied loosely to bone produced no effect, indicating that the response is dependent upon the mobilization of calcium from the bone. Electrolysis mobilized calcium from the bone post mortem, but deposition in the dead soft tissues did not occur.

# Recent Advances in Surgery

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CONDUCTED BY ALFRED BLALOCK, M.D.

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## HYPERTENSION AND UNILATERAL RENAL DISEASE

### REVIEW OF THE LITERATURE AND REPORT OF 16 CASES

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*(Continued from the June issue)*

III. VASCULAR LESIONS AFFECTING THE KIDNEY.—A review of the literature reveals many pathologic reports of cases in which renal ischemia was produced or considerably influenced by lesions affecting the patency of the large and small renal arteries and the adjacent portion of the abdominal aorta. An accurate diagnosis is seldom made during the clinical course of these diseases but is usually established after post-mortem gross or microscopic study. The relationship of hypertension to the various vascular lesions has not been defined. In most instances renal ischemia of a localized or generalized type may ensue, but the pathogenesis of the hypertension in the given case may remain conjectural.

It is not my intention to participate in any controversial issues concerning the relation of hypertension to renal arterial disease but rather to relate in a chronological order pertinent facts and observations of the various investigators in order to establish a clearer understanding of the relation of hypertension to renal arterial disease. As early as 1836, prior to the development of blood pressure determinations, Richard Bright, in his classical work on chronic interstitial nephritis, pointed out the relation of renal disease to cardiac hypertrophy (i.e., hypertension) and recognized the thickening of the renal arterioles but did not emphasize the importance of physical changes in this process. It remained for Gull and Sutton in 1872 to demonstrate the occurrence of widespread organic disease of the smaller arteries, arterioles, and capillaries of the kidney, which they designated as "arteriocardiac fibrosis" and to consider these changes as the cause of hypertension and cardiac hypertrophy. In 1873, Johnson proposed a theory that the renal disease was primary with subsequent diffuse thickening of the walls of the smallest arteries leading to increased peripheral resistance, hypertension, and cardiac hypertrophy. Seven years later Ziegler first demonstrated the dependence of some forms of renal atrophy on arteriosclerosis of the larger renal arteries (arteriosclerotic contracted kidney).



Credit is due Jores in 1904 for first differentiating such forms of renal atrophy which were commonly called chronic interstitial nephritis but which were actually caused by arteriosclerosis of the smaller renal blood vessels. Four years later Jores advanced the theory that the diffuse fine granular kidney in chronic interstitial nephritis was also of a vascular atherosclerotic origin and that this type of renal atrophy was always accompanied by a marked hypertrophy of the left ventricle. Allbutt and Huchard stressed the frequent occurrence of high blood pressure in the absence of clinically significant changes in the kidneys and arteries. Since then the literature has become replete with numerous articles dealing with hypertension and vascular lesions of the kidneys under the following headings: arteriolar sclerosis, nephrosclerosis, essential benign and malignant hypertension, etc. Despite this voluminous literature relatively little is known of the etiology of the pathologic process involved or of the pathogenesis of hypertension in the various inflammatory lesions involving the smaller arteries of the kidney, except that renal ischemia may develop as a result of the obliterative changes in the walls of these vessels.

Crabtree and Chaset recently undertook to correlate hypertension and renal vessel changes in a series of 150 nephrectomies for severe unilateral renal lesions. They were unable to establish a sufficient correlation between the two above conditions, since the number of cases with hypertension (14 cases) were too few in comparison with the large number which showed renal vessel damage. After a careful study of 1,500 pathologic sections, they classified the kidneys on the basis of vascular changes in major portion of the kidney. In the entire group, 58 cases showed definite renal vessel changes. In the infectious group of 99 cases, which comprised 66 per cent of the total group, renal vessel changes were found in 46 cases (79 per cent). The incidence of renal vessel damage in the group of chronic pyelonephritis with hydronephrosis with or without nephrolithiasis was 49.3 per cent as compared with 42.8 per cent in chronic pyelonephritis with contraction. It is interesting to note that no alteration in the renal vessels was found in 3 cases with hypertension.

*A. Arteriosclerotic Kidney.*—Allbutt attempted to clarify the confused situation which attended the clinical group, "hypertension, kidney disease, arteriosclerosis," and proposed the following classification:

1. *Hyperpiesia:* cases in which high blood pressure dominated the clinical picture with little or no renal involvement
2. *Bright's disease:* in which true renal disease occurred with or without hypertension
3. *Decreased arteriosclerosis:* in which the small atheromas of the large arteries occurred, but not necessarily associated with high blood pressure or accompanied by any significant enlargement of the heart

The latter group must be differentiated from the arteriolosclerotic (or primary contracted or hypertensive) kidney which is accompanied by marked enlargement of the heart and a very high blood pressure. However, he failed to recognize or include cases of primary hypertension with renal insufficiency. The differentiation between primary hypertensive conditions existing with and without renal insufficiency and the recognition of pathologic criteria of two types of vascular renal disease corresponding to these two clinical forms were established by Volhard and Fahr. They considered only arteriosclerosis to be associated with simple or benign hypertension; whereas, a combination of atherosclerosis with inflammatory renal changes was believed to be responsible for the malignant form of hypertension (the so-called "*Kombinations Form*"). Subsequent contribution to the various phases of arterial and arteriolar changes were made by Herxheimer, Lohlein, Fahr, Volhard, and others.

It is generally agreed that a reciprocal relationship exists between hypertension and renal arteriosclerosis, but the question as to whether hypertension is the cause or the result of renal arteriosclerosis remains a moot one. Renal arteriosclerosis may involve the large and small arteries and arterioles, but in some cases the predominant changes occur in the arterioles, and in other cases in the larger interlobular arteries. Involvement of the arterioles alone is a rare phenomenon according to Kimmelstiel and Wilson. The preponderance of clinical and pathologic observations lends support to the view of Aschoff, Fahr, and Kimmelstiel that hypertension serves as an accelerating factor in the development of arteriosclerosis.

*B. Localized Arteriosclerotic Disease of the Renal Arteries.*—In the Harvey Lecture of 1938 Goldblatt stated that in a few cases of hypertension without arteriosclerosis, severe sclerosis and narrowing of the orifice or lumen of the main renal arteries or the larger extrarenal branches may occur and produce renal ischemia. Our knowledge of the relation of hypertension to localized arteriosclerotic changes in the renal arteries has been greatly enhanced by the contributions of Leiter, Blackman, Oppenheimer and associates, Stewart, and others. Leiter reported a case of chronic hypertension associated with arteriosclerotic occlusions of the main renal arteries, renal insufficiency, retinal arteriosclerosis, and contracted kidneys. Blackman studied the pathologic changes in the renal arteries in 50 cases of essential hypertension as compared with a control series of 50 nonhypertensive patients balanced as to age and sex incidence. Narrowing of the main renal arteries at or near the aorta was found in 86 per cent of the hypertensive subjects. The narrowing was quite pronounced (i.e., almost total occlusion in 54 per cent; of a less pronounced degree, i.e., constriction of lumen to 1.5 mm. or less in 32 per cent; and no significant constriction was observed in 14 per cent). On the other hand, appreciable narrowing of the main renal arteries was found in only 10 per cent of the control series.

Oppenheimer, Klemperer, and Moschkowitz observed hypertension in 15 (83 per cent) of 18 cases of unilateral narrowing of the renal artery and found arteriosclerosis and arteriolar sclerosis of the kidneys in each of the 15 cases. The relative frequency of hypertension was greater in this specific type of unilateral renal disease than in the two other types studied; viz., 32 per cent in unilateral hydronephrosis (with chronic pyelonephritis) and 23 per cent in unilateral congenital hypoplasia. They were of the opinion that the intrarenal arterial changes preceded the arteriosclerosis of the main renal arteries. Furthermore, arteriosclerosis of the aorta was present in 13 of the 15 cases with hypertension which compared favorably with the high incidence of hypertension (60 per cent) in 100 control cases of arteriosclerosis of the aorta.

Stewart recently described a case of severe hypertension in a 37-year-old male due to arteriosclerotic narrowing of the orifices of the renal arteries. The kidneys showed marked atrophy and histologic changes suggestive of chronic glomerular nephritis but no signs of arteriolar sclerosis. A fatal case of hypertension caused by a large localized arteriosclerotic plaque narrowing the orifice of the renal artery of a solitary acquired kidney in a 57-year-male was reported by Freeman and Hartley. The other kidney had been removed two years previously following a rupture and was histologically normal. Saphir and Balinger recently reported 3 cases of severe arterial hypertension secondary to unilateral stenosis of the orifice of the renal artery with consequent ischemia of one kidney. In 2 of these cases autopsy revealed unilateral malignant nephrosclerosis in the contralateral kidney.

*C. Arteriolosclerosis of the Kidney.*—There is a unanimity of opinion concerning the fact that renal arteriolosclerosis is the cause of hypertension despite the fact that rare cases of renal arteriolosclerosis without hypertension have been reported by Lohlein, von Monakow, Fahr, and Kimmelstiel. The incidence of renal arteriolosclerosis in cases of cardiac hypertrophy with hypertension is very high; the figures vary: 90 per cent (Bell and Clawson), 97 per cent (Herxheimer and Schulz), and 100 per cent (Fishberg). Kimmelstiel and Wilson have pointed out that these figures are based on the quantitative estimation of arterial damage and hence are open to question. They maintained that less than 50 per cent of the cases show a completely diffuse arteriolosclerosis. They believed that Goldblatt's experiments may be considered as positive evidence in support of the contention that obstruction to kidney circulation is a primary factor in the production of hypertension.

Volhard and Fahr proposed a classification of hypertension based on the degree of arterial and arteriolar changes in the kidney. They designated as:

1. Essential Hypertension, cases in which renal vascular changes are absent.

2. Benign Nephrosclerosis, cases in which hypertension is secondary to arterial and arteriolar sclerosis.

3. Malignant Nephrosclerosis, cases characterized by specific arterial lesions in the kidney, namely productive endarteritis and necrotizing arteriolitis.

Later Fahr designated a subgroup of benign nephrosclerosis characterized by focal glomerulitis and elevated nonprotein nitrogen in the blood as a decompensated form of benign nephrosclerosis.

This classification appeared to be inadequate because of its failure (a) to reconcile the clinical and pathologic findings in the three groups, (b) to explain the borderline cases, and (c) to account for the characteristic arterial changes being present in other conditions; i.e., contracted pyelonephritis, diffuse glomerulonephritis, etc. The need for accurate histologic criteria consistent with the various clinical states and for a closer correlation between the degree of renal impairment and pathologic changes soon became apparent. As a result of an intensive clinical and pathologic study, Kimmelstiel and Wilson have proposed several modifications of this classification which have received popular recognition. They maintained that benign hypertension and benign nephrosclerosis may show a parallel development but in the early stages are not etiologically related and in the later stages exhibit a reciprocal relation. They believed that malignant hypertension and malignant nephrosclerosis show a definite correlation and considered malignant hypertension as a primary generalized vascular disease of which the malignant nephrosclerosis of Fahr represents the "renal end stage." They regarded endarteritis in its diffuse form as the most characteristic histologic sign of malignant hypertension. Arteriolitis (arteriolar necrosis) is more closely related to terminal renal failure than to hypertension per se. As the result of a study of the relation of periarteritis nodosa to malignant hypertension, they suggested that two factors are necessary for the development of malignant hypertension; namely, pre-existing hyperactivity or sensitivity of the arteries on which is superimposed a precipitating factor, allergic or otherwise.

Moritz recorded 3 cases with essential hypertension and renal arteriolar sclerosis in which the lesion was limited to one kidney. Weiss, Parker, and Robb described a case of unilateral bleeding in a 27-year-old male which was diagnosed preoperatively as a malignant tumor of the kidney. At operation, sixty-seven days before death, the kidney was removed and a diagnosis of malignant nephrosclerosis was made. A comparison of the sections of both kidneys showed a striking increase in the extent and severity of the productive endarteritis in the non-operated kidney during this interval.

D. *Thrombosis and Embolism of Renal Arteries.*—Little is known of the role of thrombosis of the renal artery in the production of hypertension. Welty recently analyzed the clinical features of 11 cases of

renal artery thrombosis which is so frequently mistaken for an acute abdominal catastrophe. Hypertension was present in every case. It is likely that the hypertension may be of the transitory type in the early congestive stage of renal artery thrombosis or entirely absent when acute total suppression of urine results from the thrombosis. Hypertension may develop in the later stages of renal artery thrombosis or embolism when ischemic changes in the kidney develop subsequent to occlusion or canalization of the affected artery. The relation of hypertension to thrombosis and embolism of the renal artery will undoubtedly be clarified when more is known of the late or delayed effects of such vascular lesions upon the kidney.

Fishberg noted the development of a transitory hypertension associated with embolism of the renal artery in a patient admitted with a diagnosis of myocardial infarction. The blood pressure remained about 100/60 mm. for two weeks until the patient developed the classical picture of infarction of the left kidney when the blood pressure rose to 155/108 mm. The blood pressure remained at this high level for five days and then gradually declined to the previous level.

*E. Infarct of the Kidney.*—A review of the literature reveals a difference of opinion regarding the effect of renal infarct upon the production of hypertension. Experimental evidence fails to substantiate the claim that renal infarction due to multiple emboli gives rise to hypertension. This is confirmed by the negative results reported by Senator in 1911 following the injection of liquid paraffin into the renal arteries; by Cash in 1924 following injection of insoluble Berlin blue and by Apfelbach and Jensen in 1911 following injection of charcoal particles. The clinical evidence supporting this contention is likewise scant. Boyd and Lewis described an unusual case in which a large infarct of the right kidney was found during a bilateral exploratory operation for a questionable adrenal tumor in a man aged 31 years. Six months after right nephrectomy, the blood pressure had decreased from 200/120 mm. to 124/84 mm., but the changes in the eye grounds persisted. They believed that the arterial disease present in the right kidney was responsible for the hypertension and the infarct was of secondary importance. Young mentioned a similar case but gave no details. Hoxie and Coggin recently reviewed 205 cases of renal infarction and found the blood pressure to be above 140 systolic and 90 diastolic in 34 per cent of the patients but stated that in no instance could it be proved that the hypertension was due to the renal infarction.

Pathologic studies of infarcted kidneys not infrequently reveal arteriolar changes in the tissues adjacent to the infarcts which lends credence to the belief that antecedent or pre-existing arterial disease is the primary factor responsible for the hypertension in cases of renal infarct. The role of spasm in the production of the arteriolar changes as well as the infarct is discussed elsewhere. However, Russell demonstrated glomerulitis in the vicinity of acute renal infarcts. Klemperer

and Otani observed necrotizing arteriolitis in the periphery of aseptic renal infarcts and attributed these changes to ischemia. Kimmelstiel and Wilson found similar glomerular and arteriolar changes in the same location but believed that these changes were the result of the action of diffusible toxins produced by the breakdown of the kidney tissue. They suggested that toxic and ischemic factors may combine to produce the alternative glomerulitis present in these cases.

Oppenheimer and his associates observed two patients who developed hypertension after they presented symptoms of renal infarct. One case terminated fatally and at necropsy a very large anemic infarct was found in one kidney and a marked congestion in the other kidney.

*F. Spasm of the Renal Arteries.*—Although the role of spasm of the small arteries and arterioles in the development of hypertension has not been definitely established, it appears that the degree of renal ischemia resulting from angiospasm of the renal arteries and its influence upon the subsequent development of hypertension are dependent upon the size of the spastic vessel and the duration of the spasm. Total infarction of the kidney infers complete obstruction of the main renal artery and is accompanied by total arrest of secretion from the affected kidney. The acute pain which accompanies these cases at the onset is due to the sudden tension of the renal capsule as a result of the acute hyperemia of the kidney. Intermittent spasm of the smaller arteries and arterioles may lead to localized areas of ischemia as a result of partial infarction, but determination of the extent of functional impairment may be difficult or impossible.

Fahr was the first to suggest the etiologic role of spasm in the development of renal arteriolar changes. Bell and Pedersen offered the following interesting hypothesis: Hypertension begins as a spastic condition of the arterioles, which in certain organs, such as the kidney, may lead to arteriosclerosis; thus a vicious cycle is set up where one condition aggravates the other. If infection supervenes, the renal arterioles and glomeruli may be severely damaged, as a fulminating hypertension with uremia develops. Kimmelstiel and Wilson are of the opinion that spasm alone does not cause arteriolitis, as evidenced by the fact that this lesion is absent in Raynaud's disease and acute eclampsia. Klemperer and Otani suggested that the endarteritis in larger vessels may produce endarteritis in corresponding arterioles, thereby producing arteriolar necrosis. They are in accord with Volhard's conception that a constitutional or acquired angiospastic factor plays a determining role in the development of the endarteritic process. Prinzmetal and Wilson have shown that the vasospastic process in malignant hypertension is universally distributed.

Volhard distinguished a specific angiospastic group of hypertensive cases in which the hypertension is not "renally conditioned": lead poisoning of the kidney and the kidney of toxemia of pregnancy. He

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others. The clinical and pathologic picture is further complicated by the fact that obliterative endarteritis occurs in other diseases and organs; i.e., chronic nephritis, tuberculosis, syphilis, tumors, etc. In view of the definite relation which has been established between hypertension and the obliterative arteriolar lesions of chronic pyelonephritis and arteriosclerosis by recent clinicopathologic studies and experimental investigation, it is logical to assume that the obliterative lesions of these rare primary lesions of the smaller renal arteries may produce ischemic changes in the kidney and subsequently hypertension. We may look forward to seeing more frequent reports of hypertension associated with primary obliterative lesions of smaller renal arteries in the immediate future.

Volhard mentioned syphilitic endarteritis as one of the causes of hypertension. Fishberg stated that hypertension may occur in the rare cases of amyloid contracted kidney due to syphilis and conceivably in rare sclerogummatous form of renal syphilis. Rich noted hypertension in 12 of 19 cases of syphilitic nephritis.

2. *Thromboangiitis Obliterans of the Kidney*: Jaeger has described a visceral form of thromboangiitis obliterans in association with the typical vascular manifestations in the extremities. He demonstrated that the visceral lesions are characterized by thrombotic occlusion with organization and appear to involve the veins as well as the arteries. Leiter recently reported a unique case of acute hypertension, with normal renal function, due to thromboangiitis of the smaller renal arteries in a tabetic patient.

3. *Periarteritis Nodosa*: Periarteritis nodosa is a relatively uncommon vascular disease whose pathologic features were first described by Rokitsansky in 1852 and whose clinical aspects were correlated by Kussmaul and Maier in 1866. The characteristic symptoms of this disease are fever, anemia, polymyositis, polyneuritis, gastrointestinal disturbances, renal lesion simulating nephritis, retinal arterial changes, cerebral manifestation simulating encephalitis, and hypertension. These symptoms are due to the widespread necrotizing and obliterating vascular lesions. The disease is of unknown etiology, but the nature and diffuseness of the lesions suggest an infectious background. The chief pathologic change is a patchy destruction of the media of the small arteries. Aneurysmal dilatations may develop in the weakened walls of the vessels, usually at the base of a branching vessel. The lumen of the vessels is frequently narrowed or obliterated by the scars.

The frequent involvement of the kidney in this disease was first emphasized by Gruber who found renal changes in 74 per cent of the 108 collected cases and later by Arkin who found renal changes in 80 per cent. The usual signs and symptoms of a renal lesion in this disease are strongly suggestive of a nephritis which accounts for the frequent incorrect clinical diagnosis of "hemorrhagic nephritis." In several cases the erroneous diagnosis of an "acute surgical kidney" (i.e., peri-



maintained that the changes which occur in the kidney of toxemia of pregnancy are due to toxic substances of extrarenal origin which cause excessive vascular spasm, resulting in some cases in typical endarteritic changes in the vessels of the kidney and ultimately hypertension. The tubular changes in such a kidney are considered part of a general vasoconstriction.

Some writers, particularly the Germans, attach particular significance to the role of angiospasm in pathogenesis of various vascular disturbances; i.e., cerebral apoplexy, renal infarction, embolism, etc. Recent investigations on the pathologic substratum of renal infarcts tend to prove that an antecedent circulatory disturbance such as embolism is not an absolute prerequisite in the development of renal infarct. According to Fahr a toxic spasm of the renal vessels of sufficient duration may lead to degenerative changes in the parenchyma varying from a localized area of ischemia to total cortical necrosis. On the basis of clinical and experimental investigations, Westphal maintained that a state of angiospastic ischemia may precede any apoplectic lesion and that in the kidney a temporary or brief ischemia may result from contraction of the larger renal arteries and induce bloody extravasation in the form of a hemorrhagic infarct. In 1927 Neuburger reported a series of renal infarcts without demonstrable embolism and attributed their development to the occurrence of parenchymatous lesions resulting from mild or transitory disturbances of the renal vessels. Jaffe was of the opinion that vascular spasm was responsible for the rare cases of renal and splenic infarcts in which changes in the walls of the arteries and veins cannot be demonstrated and the foramen ovale is closed. Weiss likewise reported a case of renal infarction occurring twelve days after an apoplectic stroke and accompanied by transitory speech disturbance and rapid subsidence of the paresis. He attributed both vascular lesions to an angiospastic involvement of the blood vessels.

*G. Primary Inflammatory and Obliterative Lesions of the Small Renal Arteries and Arterioles.*—A review of the literature reveals very little data or observations on the occurrence of hypertension in primary chronic inflammatory or obliterative disease of the small renal arteries and arterioles.

1. *Endarteritis Obliterans:* Volhard has stated that in rare instances primary endarteritis may serve as the cause of an angiopathic type of hypertension which is "renally conditioned." The very rare cases of granular kidney due to amyloidosis are another example of the angiopathic type of renal hypertension. The etiology of the various occlusive vascular lesions of the kidney is not clearly defined but appears to be of an infectious or toxic nature. The obliterative process may be the result of (a) the growth of tissue from or beneath the intima, (b) the organization of a thrombus, or (c) the formation of adhesions between the vessel wall and the surrounding tissues. At times it may be extremely difficult to differentiate one type of vascular lesion from the

to control bleeding, repair the wound, and drain and conserve the traumatized kidney.

There are relatively few case reports of hypertension following injuries of kidney. The case of Freeman and Hartley has been previously mentioned. Nesbit and Ratliff reported a case of hypertension associated with sclerotic and cystic nephropathy (ischemic) resulting from trauma. The patient, a male aged 32 years, had sustained a fracture of the right kidney ten years previously and nine years later developed signs of malignant hypertension. Following nephrectomy there was a marked improvement for five months followed by a progressive increase in the blood pressure. Pathologic study disclosed a cyst and marked vascular changes in the capillaries, arterioles, and larger arteries. They maintained that if the hypertension resulted from the ischemic lesions of the injured kidney, its prolonged duration led to vascular changes in other parts of the body and rendered the condition beyond repair. Schroeder and Steele reported the occurrence of hypertension in a case in which the kidney was replaced by calcified cysts. The latter was classified as an obstructive lesion but in all probability belongs to the group of post-traumatic sequelae.

Braasch, Walters, and Hammer observed hypertension in 2 cases following severe renal injury which was attributed to nephrosclerosis. These authors have emphasized the role of operative trauma and infection as etiologic factors in hypertension. They reported 14 cases in which the blood pressure was normal prior to a conservative renal operation, but hypertension developed following operation. Each case presented evidence of reduced function and persistent infection following the conservative operation and after removal of the affected kidney the blood pressure returned to normal. Widespread tissue atrophy and vascular sclerosis were found in the removed kidneys. The conservative operations or underlying condition for which such operations were performed included nephrolithiasis, nephrostomy, ureterolithotomy, nephropexy, ureterovaginal and vesicovaginal fistulas. They also observed that hypertension developed following transplantation of the ureters into the sigmoid in 2 cases. Postoperative urographic examination revealed a functionless kidney on one side, and following the removal of the affected kidney, the blood pressure returned to normal.

An important observation made by these authors was that a postoperative increase in blood pressure occurred more frequently following conservative operations for renal and ureteral lithiasis than other lesions. Hence they stress the advisability of considering nephrectomy in the presence of renal stone and extensive infection in order to circumvent the possibility of subsequent development of sclerotic pyelonephritis with hypertension.

I recently observed a case of postoperative hypertension develop in a male patient, 52 years of age, with a left renal calculus and left

nephritic abscess, calculus, pyonephrosis, neoplasm, etc.) was made and exploratory operation performed, the true diagnosis being made at necropsy. Wever and Perry reported a case in which death followed an operation for perirenal hemorrhage and collected 8 cases in which death was due to renal or perirenal hemorrhage.

Bernstein found that hypertension was present in the majority of cases where the blood pressure was recorded. Spiegel observed hypertension in 9 of 15 cases. It is surprising that the incidence of hypertension is not greater in view of the generalized nature of the disease and the degree of vascular resistance offered by such an extensive disease process. It is difficult to evaluate the role of renal ischemia in the development of hypertension for, unfortunately, no data are available on the incidence of hypertension in cases with or without demonstrable renal changes. However, a review of literature reveals that hypertension is an almost constant finding in cases with renal changes.

*H. Traumatic Injuries of the Kidney.*—There is little information available concerning the role of traumatic injuries of the kidney in the pathogenesis of hypertension. Too frequently the attending surgeon or urologist focuses his entire attention on the immediate condition following the rupture and fails to consider the late sequelae of traumatic injuries of the kidney. In the minor or least serious types of renal trauma, such as contusions or small cortical, capsular or perinephritic tears accompanied by slight intrarenal or extrarenal hemorrhage, repair of the wound is initiated early and progresses at a rapid rate, being fairly advanced after one week and the ultimate effect on the kidney function is scarcely detectable. However, in the more serious types of renal injuries, such as parenchymal tears, fragmentation and rupture of the vascular pedicle accompanied by extensive hemorrhage in and around the kidney or by extravasation of urine, the degree of renal damage and dysfunction is commensurate with the amount of kidney tissue destroyed and the nature of the reparative process. Ordinarily connective tissue fills in the spaces between the torn edges of the wound, but in severe injuries a variety of pathologic changes may occur in and about the kidney long after the primary injury and lead to renal ischemia or serious impairment of renal function. Among these changes, which may appear singly or in combination, are included: fibrosis, necrosis, infection, hydronephrosis, calculi, cystic degeneration, calcification, thrombosis, infarction, constriction of blood supply, perinephritis due to hemorrhage, extravasation, or infection, etc. One cannot emphasize too strongly the value and importance of early surgical intervention in cases of extensive injuries to the kidney in order to prevent development of such degenerative lesions which may cause serious permanent or irreparable damage, impairment of renal function, and possibly hypertension. It must be borne in mind that surgical intervention does not always imply nephrectomy but may enable the surgeon

with chronic cardiovascular disease or acute infection. Hypertension was a prominent feature in the majority of about 150 cases in the literature. Ronald and Leslie recently described a case in a 43-year-old male who had a hypertension of 260/140. At autopsy the thrombosis of the abdominal aorta was accompanied by two infarcts of the left kidney, complete thrombosis of the left renal artery and partial thrombosis of the right renal artery, and bilateral arteriosclerosis of the kidney.

2. *Coarctation of the Aorta:* Hypertension is also frequently observed in coarctation of the aorta. Rydand maintained that the elevation of blood pressure in patients with coarctation of the aorta is due to the action of pressure substances formed in ischemic kidneys as a result of interference with the blood supply of the kidney. The latter change is attributed to an increased resistance in the smaller vessels (arterioles) which receive blood from the aorta proximal to the stenosis at its isthmus. This is substantiated by animal (rat) experiments; viz., partial constriction of the aorta proximal to one or both renal arteries leads to hypertension, whereas the same type of constriction plus simultaneous bilateral nephrectomy does not result in hypertension.

3. *Aneurysm of the Aorta:* Hypertension has been reported in cases of saccular and dissecting aneurysms of the abdominal aorta and aortic arch. These pathologic lesions may cause serious impairment of the blood supply to the kidney, depending upon the point of origin and the size of the sac. Hamburger and Ferris observed high blood pressure in only 1 case in their series of 6 cases of dissecting aneurysms and commented upon the fact that while most observers consider high blood pressure to be a typical finding in this condition, they found the blood pressure to be normal or the patient to be in a state of peripheral circulatory collapse on admission. Buckley recently reported two cases of hematuria associated with dissecting aneurysms of the abdominal aorta. Hypertension was present in both cases. In 1 case rupture of the aneurysm had occurred and shock, hematuria, and fluctuating blood pressure were the cardinal symptoms.

#### IV. NEOPLASMS OF THE KIDNEY AND ADRENALS.—

A. *Kidney Tumor in Adults.* A review of the literature reveals relatively few references to the occurrence of hypertension in cases of renal or adrenal neoplasms. In 1898 Neusser was the first to emphasize the association of hypertension with hypernephromas, particularly of the adrenal gland. Subsequent contributions to this phase of the subject were made by Oppenheimer and Fishberg, Braasch and Griffin, and others. In their series of 101 cases of primary urinary tract pathology associated with hypertension, Maher and Wosika encountered only 2 cases of renal tumors.

Braasch and Griffin studied the blood pressures of 40 patients operated upon at the Mayo Clinic for renal neoplasm and found the blood pressures were within normal limits in 26 cases and increased in 14 cases.

hydronephrosis and a preoperative blood pressure of 140/90. Following operation, which consisted of nephrolithotomy, a Foley plastic repair of the pelvis and a Deming nephropexy, the patient had a stormy convalescence complicated by a fecal fistula and acute pyelonephritis. Seven months later the patient had developed a hypertension of 180/110. Pyelography revealed a small well-healed pelvis with pyelonephritic changes in the calyces. Nephrectomy was advised but refused.

### *I. Compression of Renal Vessels by Intrinsic or Extrinsic Lesions.—*

There are relatively few reports in the literature of hypertension associated with constriction of the renal arteries by intrinsic or extrinsic lesions of the renal arteries. Leadbetter and Burkland reported a case of marked hypertension (160 to 220 mm. systolic) of five years' duration in a 5½-year-old boy. The blood pressure returned to normal (96/70) following the removal of an ectopic kidney, whose main renal artery was nearly occluded by a smooth muscle tumor in the wall of the artery. Blatt and Page reported a case of hypertension in which the main renal arteries of both kidneys were constricted throughout their entire course by a retroperitoneal lymphosarcoma involving the kidneys, ureters, adrenals, abdominal aorta, and inferior vena cava. There was a moderate hydronephrosis in both kidneys due to constriction of both ureters. It appears that more than one factor may be responsible for the hypertension in each of the above cases. In the former, the anomalous position of the kidney was accompanied by abnormalities in the course, position, and size of renal vessels, which may have impaired the renal circulation and produced ischemia. In the latter, the bilateral hydronephrosis and evidences of an early glomerulonephritis were present.

Aneurysm of the renal artery is an extremely rare condition which may interfere with the renal circulation with resulting ischemic changes in the kidney. In an occasional case the aneurysm of the main renal artery may obstruct the outflow of urine, causing increased back pressure and hydronephrosis. Aneurysms of an intra- or extrarenal branch of the renal artery may produce pressure on one or more calyces, resulting in hydrocalicosis and even stone formation. Onel and Valencia observed a case of renal aneurysm in a patient with repeated gravidie nephropathies and persisting hypertension. Howard, Forbes, and Lipscomb recently reported a case of aneurysm of the left renal artery in a 5-year-old child with persistent hypertension successfully treated by nephrectomy.

### *J. Miscellaneous Vascular Lesions.—*

1. *Thrombosis of Abdominal Aorta:* Hypertension has been recorded in a group of rare primary vascular lesions of the aorta which produce or are accompanied by secondary changes in the kidneys or the renal arteries. Thrombosis of the abdominal aorta is a rare but invariably fatal condition occurring in elderly people and is usually associated

adrenal secretion in two tumors and obtained similar results in a subsequent examination of three other renal adenocarcinomas, employing his new chemical method for determining the amount of adrenal cortex secretion.

Dean found that hypertension occurred in practically every one of a small group (approximately 10 cases) of papillary tumors of the kidney pelvis and ureter in which obstruction, infection, and destruction of the renal parenchyma were marked. There was no reduction in the hypertension following operation.

Braasch, Walters, and Hammer observed hypertension in 6 cases of epithelioma of the renal pelvis, and following nephrectomy, the blood pressure returned to normal in only 1 case.

It is surprising to note that little or no reference was made in any of the above articles to the possible role of ischemia in the production of hypertension in cases of renal neoplasms. Obviously, varying degrees of renal ischemia may occur as a result of vascular changes produced within the kidney by the tumor. These changes may manifest themselves in any of the following ways: (a) compression of the blood vessels in the renal parenchyma adjacent to the tumor; (b) compression of the vascular pedicle by the tumor; (c) compression, distortion, or angulation of the vascular pedicle by the displaced kidney; (d) vascular changes in the parenchyma induced by infiltrating tumor tissue; (e) thrombosis of the large or small renal vessels of one or both kidneys due to infiltration by tumor cells or to stasis. Undoubtedly future studies of renal tumors will throw some light on the relation of the pathologic features of the tumor to hypertension.

There are no data available at present to suggest any relation between hypertension and the development of recurrences or metastases from primary renal carcinomas, including hypernephroid tumors in adults or secondary metastatic nodules in the kidney from neoplasms elsewhere in the body. However, there are some data on hand concerning the relation of hypertension to recurrences and metastases in Wilms' tumors. In 1938 Bradley and Pineoffs reported 5 consecutive cases of Wilms' tumor accompanied by hypertension and observed that in 2 cases the blood pressure decreased following nephrectomy but rose again after recurrence of the tumor.

CASE 14.—(G. U., No. 896.) W. T., 52 years of age, white, male, married, business executive, was admitted to the Sinai Hospital on Mar. 21, 1930, complaining of hematuria. The patient had been in good health until four years before when he had passed blood for the first time. Hematuria recurred six months and again six days before admission. There were no other urinary symptoms present.

Abdominal examination revealed a palpable, but not tender, right kidney. Examination of the urine revealed a faint trace of albumin and many red blood cells, and a moderate number of pus cells. His blood urea was 39.55 mg. per cent. On cystoscopy blood was seen escaping from the right ureteral orifice. Pyelogram revealed compression and elongation and partial obliteration of the lower and middle major and minor calyces. A diagnosis of renal neoplasm was made.

In several cases the hypertension was present for several years prior to the onset of symptoms. They believed that the hypertension in these cases was of the essential type. Following the removal of the kidney tumor, the blood pressure remained stationary in most cases and showed a slight decrease in a comparatively few cases. In the same clinic Horton and Morlock compared the hypertension occurring in cases of hypernephroma with that in other types of renal tumor but failed to find an increased incidence in hypernephroma or any difference in postoperative reduction in blood pressure. A systolic blood pressure of more than 200 mm. of mercury was present in 4 patients who were living five years after operation. Based upon the above reports, Braasch and Griffin concluded that hypertension was of little prognostic significance in renal neoplasms.

Subsequently Braasch, Walters, and Hammer reported 38 instances of hypertension (27.7 per cent) in a series of 137 adenocarcinoma of the kidney, including hypernephroma. They attached much significance to the factor of age in explaining the high incidence of hypertension in this group, since 87 (63.5 per cent) of these patients were 50 years of age or more. The postoperative course of 43 patients operated upon for hypernephroma was carefully studied. Preoperative hypertension was present in 21 of these cases. Following operation the blood pressure returned to normal in 9 cases, was temporarily reduced but subsequently became elevated in 3 cases, and was uninfluenced in 9 cases.

Crabtree and Chaset reported 6 cases of hypernephroma with preoperative hypertension. Following nephrectomy there was a slight improvement in blood pressure in only 1 case. They observed that a higher degree of hypertension usually occurred in cases of hypernephroma as compared to other severe unilateral renal lesions and attributed this change to the age factor.

Neusser advanced the theory that hypertension in cases of hypernephroma was caused by the absorption of some secretion from the tumor cells of suprarenal origin. Braasch and Griffin pointed out that there are clinical evidences of other abnormalities in the vascular system; i.e., fever, increased pulse rate, and telangiectasis, which may be attributed to the absorption of some specific substance. These absorptive vascular phenomena are not to be confused with vascular changes resulting from mechanical obstruction of the venous circulation by the tumor; i.e., varices of the abdominal wall and legs, left-sided varicocele. There are conflicting reports concerning the results obtained by chemical examination of renal tumor tissue for adrenal cortical elements which might be responsible for the hypertension as well as other symptoms; i.e., fever, pigmentation of skin, and changes in blood volume. In 1931 Rowntree, Greene, Swingle, and Pfiffner made biologic assays of hypernephroid tumors and found the cortical hormone (adrenal cortex extract) to be comparable in amount to that present in the normal adrenal cortex. In 1932 Kendall failed to find any evidence of

the hospital about eight months previously for treatment of diabetes mellitus. The patient was put on dietary treatment with insulin, but he failed to carry out this regime carefully. He had lost considerable weight and was extremely weak. The patient also complained of diurnal frequency and nocturia with occasional dysuria. About five months before, he had had hematuria which recurred on the afternoon prior to admission.

Physical examination revealed the patient to be thin and emaciated. Neither kidney was palpable, but tenderness was present in the left upper and lower quadrants. Cardiac hypertrophy was present. The blood pressure was 220/110. Ophthalmoscopic examination showed fairly well advanced hypertensive changes. Urine showed 4+ sugar and many red blood cells. Blood urea was 38.35 mg. per cent; blood sugar was 244 mg. per cent. Cystoscopy and pyelography were performed and a diagnosis of left renal neoplasm (hypernephroma) was made. X-ray studies of the chest and long bones failed to reveal any evidences of metastasis. The patient's diabetic condition was regulated by dietary regime and insulin therapy. On July 1, 1932, a left nephrectomy was performed under spinal anesthesia. The patient made an uneventful recovery and was discharged from the hospital on Aug. 18, 1932.

Following his operation, the blood pressure gradually fell and remained at 162/88. The patient returned to his family physician for observation and treatment of his diabetic condition. For the next eight months his blood pressure remained stationary at the above level. About July, 1933, the patient died suddenly of cardiac failure.

The pathologic specimen showed a large, irregular nodular tumor occupying the upper two-thirds of the kidney. The tumor was only partly encapsulated and in several areas appeared to infiltrate the surrounding kidney tissue. The vascular pedicle contained no tumor infiltration. Histologic study revealed an alveolar type of hypernephroma. Acute and chronic inflammatory changes were found in the presumably normal kidney tissue and the blood vessels in the same area showed only scant changes (grade 1+).

*B. Kidney Tumors in the Young.*—Daniel has recently made a comprehensive study of the hypertensive factor in 18 cases of Wilms' tumor in children between the ages of 8 months and 9 years. For children of this age period he considered a systolic blood pressure below 10 mm. of mercury as normal, 110 to 125 mm. as moderately elevated, and above 125 mm. as extreme elevation. Using these criteria, he found 4 cases with normal blood pressure, 6 with moderate elevation, and 8 with extreme elevation. Braasch, Walters, and Hammer observed definite hypertension in 5 of 18 cases of Wilms' tumor. One may infer from these findings that hypertension is a frequent but not constant finding in cases of Wilms' tumor.

Koons and Ruch recently reported a case of hypertension in a 7-year-old girl with a Wilms' tumor of the left kidney relieved by nephrectomy. The preoperative blood pressure was 190/155 and on the eleventh postoperative day was 116/76. Subsequent postoperative findings were unfortunately not recorded.

Daniel maintained that the hypertension of these cases was the result of renal ischemia, produced mechanically by the tumor, thus differing from Bradley and Pinecoff's who attributed the elevated blood pressure



On Mar. 22, 1930, a right nephrectomy was performed and a tumor was found in the lower pole of the right kidney. The patient made an uneventful recovery and was discharged from the hospital on Apr. 8, 1930.

His blood pressure varied between 180 and 184 systolic and 110 to 112 diastolic prior to operation. At the time of discharge from the hospital, his blood pressure had fallen to 154/82. The patient was followed by his family physician for five years. For the first three years after operation his general health was excellent and his blood pressure did not exceed 156/84, but in the next two years his blood pressure became elevated. The patient died five years after operation of cerebral hemorrhage.

The pathologic diagnosis was (1) chronic pyelonephritis, (2) chronic parenchymatous nephritis, and (3) hypernephroma with hemorrhagic extravasation and necrosis. The vascular changes throughout the renal parenchyma were relatively mild (grade 1+).

CASE 15.—(G. U., No. 1341.) A. W., white, male, 62 years of age, married, merchant, was admitted to the Sinai Hospital on Feb. 6, 1933, complaining of hematuria. His mother had died at the age of 65 years of carcinoma of the stomach. The patient was in good health until two years previously, when he developed intermittent pain in the left kidney region, accompanied by hematuria lasting three to four days. There were no urinary or general constitutional symptoms. About one year before admission he had hematuria which lasted for two days and was unaccompanied by other symptoms. He had hematuria again ten days before admission. He had lost seven pounds in the past year. Two days before admission he had had a recurrence of pain in the kidney region which was present at the time of admission.

Examination revealed slight tenderness over the left kidney. Neither kidney was palpable. Blood urea was 27.56 mg. per cent. Intravenous phthalein was 33 per cent for the first hour and 20 per cent for the second hour. Urine was negative except for 8 to 10 red blood cells and an occasional pus cell on microscopic examination. Cystoscopy and pyelography revealed a normal kidney pelvis on the right, but on the left there were compression and distortion of the upper and middle major calyces, suggestive of a renal neoplasm.

On Feb. 7, 1933, a left nephrectomy was done under ether anesthesia. The kidney contained a tumor measuring 3 cm. in diameter which compressed and distorted the middle major and upper major calyces of the left kidney. A calculus about the size of a lima bean was found in the middle major calyx. The patient made an uneventful recovery and was discharged from the hospital on Feb. 21, 1933. Upon admission to the hospital, the patient's blood pressure was 168/86; upon discharge the patient's blood pressure had fallen to 140/80. Subsequent blood pressure determinations were made by his family physician who stated that during the period of observation for one year following operation, his blood pressure did not rise above 144/80.

The pathologic diagnosis was adenocarcinoma of the kidney (papillary type). The tumor tissue showed extensive hemorrhagic extravasation with some necrosis. In the kidney tissue adjacent to the tumor, the tubules and glomeruli were atrophic and necrotic. The remainder of the kidney presented evidences of degenerative changes varying from cloudy swelling to actual necrosis of tubules and glomeruli with moderate fibrotic changes in the walls of the smaller blood vessels (grade 1+).

CASE 16.—(G. U., No. 12325.) J. S., 63 years of age, white, male, married, tailor, was admitted to the Sinai Hospital on June 11, 1932, complaining of pain in the lower left quadrant, vertigo, and dizzy spells. The patient had been in

personal case. The pathologic findings were: carcinoma, 13; cortical adenoma, 4; hyperplasia, 8; tumor (type not stated), 3; no pathologic data, 2.

According to these authors, hypertension is a frequent finding in cases of diffuse or circumscribed (adenomatous) hyperplasia of the adrenal cortex. This is substantiated by the studies of Aubertin and Ambard who studied 8 cases of hypertension and found diffuse cortical hyperplasia in 4, cortical adenomas in 3, and normal gland in 1. One of the above authors found cortical adenoma in 5 cases in a series of 35 cases of hypertension as compared to 1 case of cortical adenoma in 50 consecutive necropsies on nonhypertensive subjects. Volhard described 2 unusual cases in which the clinical picture was that of diffuse nephritis with hypertension and albuminuria and in each instance the hypertension disappeared following the operative removal of a hypernephroma of the adrenal cortex.

Tumors of the medullary portion of the adrenal gland are encountered less frequently than the cortical tumors and may be classified in two groups: benign and malignant. The benign tumors are derived from the formative cells of the sympathetic ganglions according to Oppenheimer and Fishberg and are divided into 3 types: (1) sympathoblastoma, composed of immature sympathoblasts; and (2) ganglioneuroma, composed of relative mature sympathetic cells and more differentiated than Group I; and (3) paraganglioma (or pheochromocytoma) composed of mature chromaffin cells. The malignant tumors are considered under the heading of neuroblastoma (or neurocytoma) and are usually diagnosed after early extensive metastases have occurred in skull, orbit, and long bones in children (Hutchinson type) and in the liver and lungs in adults (Pepper type).

Hypertension is rarely observed in cases of ganglioneuroma, neuroblastoma, and metastatic tumors of the adrenal but is an almost constant concomitant of paraganglioma. The clinical features of paraganglioma, which were first emphasized by Labbe and his associates, in 1922, are characterized by attacks of paroxysmal hypertension accompanied by other vasomotor phenomena; viz., headache, pallor, flushing, tachycardia, sweating, nervous apprehension, dyspnea, etc. This symptom complex is frequently referred to as the "suprarenal sympathetic syndrome" (Belt and Powell) and is caused by the hyperfunctioning adrenal tumor. The paroxysms of hypertension may be precipitated by undue physical or mental exertion and experimentally by the "cold pressor test."

When the presence of the tumor passes unrecognized for months or years, the attacks of paroxysmal hypertension increase in severity and frequency and permanent vascular and renal changes develop. The blood pressure remains high and paroxysmal attacks are superimposed. Cardiac hypertrophy, arteriosclerosis, retinal changes, and evidences of

not to interference with the renal blood supply but to the fact that the tumor tissue, like renal tissue, possessed the property of causing an elevation in blood pressure when altered by certain types of damage. Koons and Ruch likewise attributed the hypertension to interference with renal circulation by invading tumor tissue at the renal pedicle. They also suggested that the neoplastic mass surrounding the kidney may act in the same manner as the cellophane envelopes used by Page to produce experimental hypertension. Daniel observed a striking reduction in blood pressure following irradiation in 3 cases with extreme hypertension, and following nephrectomy the blood pressure remained at normal levels. The beneficial effect of irradiation was thought to be due to a reduction in the size of the tumor mass and the consequent lessening in the amount of ischemia. He found that when the hypertension was of sufficient duration to have allowed the development of sclerotic changes in the arterioles of the presumably good kidney, neither irradiation nor nephrectomy had a beneficial effect upon the hypertension.

Daniel explained the hypertension associated with local recurrence in the 2 cases of Bradley and Pincoffs and in 1 personal case on the basis of renal ischemia resulting from tumor growth about the vascular pedicle of the remaining kidney. Furthermore he found that the predominant cell type of Wilms' tumor, epitheloid, mesoblastic or mixed, had no influence upon the presence or absence of hypertension. He concluded that hypertension in cases of Wilms' tumor is of grave prognostic significance and is probably indicative of tumor growth in the region of the vascular pedicle.

C. *Adrenal Tumors*.—Tumors of the adrenal gland have recently become the subject of renewed interest and much study on the part of pathologists, clinicians, and surgeons. For practical purposes they may be classified into two main groups: (1) adrenal cortical tumors, derived from the mesoderm of the wolffian body, and (2) adrenal medullary tumors, originating in structures giving rise to the sympathetic nervous system. The most common tumor of the adrenal is a hyperplasia of the cortex which has a tendency to produce changes in the sexual characteristics of the affected person (the so-called "*syndrome g nito-surr nal*" of Gallais or "*adrenal hirsutism*" of Krabbe).

The earliest reference to the occurrence of hypertension in cases of adrenal tumors was made by Neusser, in 1898. He reported 2 cases in which the clinical course was typical of nephritis, but at necropsy an adrenal neoplasm (carcinoma) was found and the kidneys and arterioles appeared to be normal. In a comprehensive review of the literature by Oppenheimer and Fishberg in 1924, only 15 cases of chronic nonnephritic hypertension associated with adrenal tumors were collected; 11 cases were cortical tumors and 4, medullary (paragangliomas). In 1938 Nuzum and Dalton collected 29 cases of hypertension ascribed to hyperplasia or tumor of the adrenal cortex and added 1

have gained a clearer understanding of the anatomic and clinico-pathologic problems arising from the diverse types of congenital malformation in the urinary tract and the complexity of the development of the permanent kidneys. Excellent classifications of the anomalies of the urinary tract have been proposed by Young, Hinman, Gutierrez, and others and a further discussion of same is intentionally omitted.

A. *Anomalies of the Kidney.*—Suffice it to say that practically every congenital malformation in the urinary tract, sooner or later, exerts some deleterious effect upon the integrity and function of the kidneys. Congenital malformations in the lower urinary tract may be responsible for a variety of pathologic changes in one or both kidneys, the most common change being hydronephrotic atrophy secondary to obstructive defects.

The literature abounds with numerous reports which confirm the fact that every congenital anomaly of the kidney proper, its excretory apparatus or its vascular supply, is a potential clinicopathologic entity. Some anomalies of the kidney exhibit a greater tendency to secondary changes than others. This is particularly true of anomalies of form (fusion types), of position (ectopic kidney), and of structure (aplastic, hypoplastic, and cystic kidneys). The intrinsic kidney lesion may manifest itself either as (1) extensive histologic changes (i.e., embryonic, sclerotic, or calcified glomeruli and tubules which occur in aplastic or hypoplastic kidneys as a result of defective development of the fetal kidney or cystic degeneration in polycystic kidney); or (2) hydronephrotic atrophy secondary to congenital obstructive lesions in the upper or lower urinary tract; or (3) renal atrophy secondary to anomalous blood supply; or (4) various types of inflammatory lesions of the parenchyma due to acquired infections; or (5) calcuosis secondary to obstruction or infection. The secondary changes within the anomalous kidney may be so extensive as to impair seriously or to destroy totally the renal function. Not infrequently the opposite and presumably normal kidney shows signs of impaired function due to the additional strain imposed upon it by injured anomalous mate. It is highly probable and indeed possible that the secondary changes within the anomalous kidneys lead to varying degrees of renal ischemia and subsequently hypertension with greater frequency than is generally recognized at present.

The probability of hypertension associated with congenital anomalies assumes greater clinical significance when one considers that 40 per cent of pathologic conditions of the kidney and ureter are due to congenital anomalies of the kidney according to Gutierrez. In a series of 282 cases of hydronephrosis in infants and children, Campbell found the condition was secondary to an upper urinary tract anomaly in 193 cases (68.8 per cent) and in 508 cases of persistent pyuria in young children he found a total of 206 anomalies of the upper urinary tract in 179 patients (30 per cent).

renal damage appear. Patients with paragangliomas are extremely poor surgical risks and not infrequently exhibit a tendency to sudden death following a major or minor surgical procedure. In the latter cases, the cause of death is determined only by the finding of an adrenal medullary tumor at necropsy. I recently performed a bilateral exploratory of the adrenal glands in a case of paroxysmal hypertension but failed to find any *pathologic changes* in or about the adrenal glands.

In 1938 MacKenzie and McEachern collected 20 operative cases of paraganglioma from the literature. Walters and Kepler reported 4 cases of paraganglioma from the Mayo Clinic; 3 of these cases, which include the cases previously reported by Mayo and Walters, were successfully operated upon and no further paroxysms of hypertension have occurred; the fourth case was diagnosed at autopsy. Similar good results were obtained by Shipley, the Porters, MacKenzie and McEachern, and others.

In 1938, Nuzum and Dalton stated that approximately 85 cases of pheochromocytoma have been reported in the literature and added 1 case successfully treated by operation. A clinical diagnosis was made in only 20 cases. Blood pressure was not recorded in 36 cases and was said to be normal in 3 cases. In the group of 41 cases in which hypertension was found, the paroxysmal type was observed in 22 and the constant type in 19; evidence of kidney change was present in 3 cases of which 2 were atherosclerosis.

Hypertension has been observed in association with other adrenal conditions. Ferrara reported a case associated with a hematic cyst of the left adrenal. Demole and Rutishauser described a case of paroxysmal hypertension due to adrenal tuberculosis.

Oppenheimer and Fishberg maintained that there is no evidence based on experimental studies or chemical and pharmacologic examination of the blood to support the theory of Vaquez that the hypertension in cases of adrenal tumors is caused by a hyperpinephremia. The presence of large amounts of epinephrine in the tumor tissue, as demonstrated by microchemical and biologic methods, has been reported by Orth, Belt, and Powell, and others. The exact mechanism responsible for production of hypertension in cases of adrenal tumors has not definitely been established but in all probability is intimately associated with vascular changes produced in kidney and other parts of the body by the absorption of the increased epinephrine present in the tumors. Confirmatory evidence of this view is found in the relatively high incidence of arteriolosclerosis and arteriosclerosis in cases of paragangliomas and the frequent occurrence of diffuse hyperplasia and circumscribed adenomas in the adrenal cortex in patients with hypertension.

V. CONGENITAL ANOMALIES OF THE URINARY TRACT.—The relation of hypertension to congenital anomalies of the urinary tract, especially of the kidneys, must remain unsettled until more clinical observations and pathologic data are recorded. It is only within recent years that we

have gained a clearer understanding of the anatomic and clinico-pathologic problems arising from the diverse types of congenital malformation in the urinary tract and the complexity of the development of the permanent kidneys. Excellent classifications of the anomalies of the urinary tract have been proposed by Young, Hinman, Gutierrez, and others and a further discussion of same is intentionally omitted.

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Volhard regarded congenital hypoplasia of the kidney as a frequent cause of hypertension. Leiter has emphasized the fact that hypertension appeared to be a characteristic feature in cases of unilateral hypoplasia and allied developmental anomalies of the kidney even in the absence of severe renal insufficiency. He also called attention to the following striking but paradoxical situation; viz., the absence of hypertension in about 75 per cent of cases of renal dwarfism and rickets, diseases observed in children and associated with congenital dilatation of the urinary tract, and severe fibrotic atrophy of the kidneys.

In the case reported by Leadbetter and Burkland, the affected kidney, responsible for the hypertension, was situated in the pelvis, causing constriction and narrowing of the renal vessels in addition to partial occlusion of the main artery by a piece of aberrant muscle. Removal of this kidney resulted in a cure. Leiter reported a nonoperative case of hypertension associated with congenital asymmetrical atrophy. Kerr described a case of severe hypertension in a young lady whose blood pressure returned to normal following the removal of a nonfunctioning embryonic (congenital hypoplastic) kidney weighing 19 Gm. Schroeder and Fish's case of hypoplasia associated with chronic pyelonephritis and arterial hypertension, which was successfully treated by nephrectomy, has been mentioned previously. Elsewhere in this paper I have called attention to the findings of Oppenheimer, Klemperer, and Moschkowitz who observed hypertension in 3 cases (23 per cent) in a series of 13 cases of unilateral congenital hypoplasia. Braasch, Walters, and Hammer found that in contrast to the high incidence of hypertension in cases of atrophic pyelonephritis, the blood pressure was normal in 5 operative cases of congenital hypoplasia.

In my series of 167 cases, neither preoperative nor postoperative hypertension was present in any of the congenital anomalous kidneys removed; viz., congenital ectopic kidney, 3 cases; double kidney, 1 case; congenital hypoplastic kidney, 1 case; horseshoe kidney (calculous pyonephrosis of one-half), 1 case. I have encountered an interesting case of hypertension (216/148) with advanced hypertensive changes in both fundi in a male, 50 years of age, who had been treated for chronic bilateral pyelonephritis for several years. A double kidney with complete duplication of both ureters was present on the right side; the upper rudimentary segment was the seat of a nonfunctioning chronic atrophic pyelonephritis. After much deliberation and with no promise of any cure or prolonged relief of hypertension, the ureter leading to this rudimentary ureter was ligated extraperitoneally rather than risk a hazardous heminephrectomy. For three months following operation, there was a slight temporary reduction in the blood pressure which varied between 180/120 and 194/140, but this was followed by a gradual return to the preoperative level in the next three months.

*B. Anomalies in the Blood Supply of the Kidney.*—There is a decided paucity of information concerning the relation of abnormalities in the

blood supply of the kidney and hypertension, particularly in cases of congenital malformations of the kidney. That such a relation may and does exist appears to be more than mere conjecture in the light of our increasing knowledge of the anatomic relations and pathologic effects of abnormal vascularization of the kidney. Anomalous renal arteries are an almost constant finding in congenital malformations of the kidney, the more pronounced the renal anomaly, the greater the variation of the blood supply. As a rule, anomalies of the renal arteries are accompanied by similar changes in venous system.

The possibilities for variations in the blood supply of the kidney are greatly due to (a) numerous peculiarities of the growth and development of the mesonephros, (b) the development of the renal vessels from the periaortic plexus which in turn originate from different embryonic arteries, (c) the vascularization of the kidney during its upward migration in the body, (d) other mechanical factors; i.e., influence of disturbances in body growth, pressure of adjacent organs, displacement by embryonic tumors, etc. Anomalous position of the kidney is one of the most important factors in the production of abnormalities in the blood supply of the kidney, for in the congenital abnormally situated kidney the blood supply arises from the nearest arterial source, and variations in the size, number, and course of the main arteries and the accessory branches are always found. The role of accessory or aberrant vessels in the production of hydronephrosis by virtue of compression of the ureter or pelvis is well recognized by urologists. This is well illustrated by Morton's case of hydronephrosis caused by an aberrant vessel and accompanied by hypertension.

It is highly probable that a direct relation exists between renal ischemia and anomalous renal vessels in some cases. Some authors maintain that the anemia from a defective arterial supply may be the important factor in the development of such renal anomalies of structure as the aplastic and hypoplastic kidneys. The evidence offered in support of this theory is based on the presence of following histologic changes within the aplastic or hypoplastic kidney; viz., sclerotic or calcified glomeruli and tubules, necrotic or functionless nephrogenic elements, varying degrees of fibrosis, or even complete absence of nephrogenic elements. Clinically these kidneys show extreme gradations of impaired renal function which may be conceivably followed by hypertension in many instances.

Varying degrees of renal ischemia may result from compression, elongation, or distortion of vascular supply of a normal or anomalous kidney by a variety of intrarenal and extrarenal lesions. For example, a congenital or acquired ptosis of the kidney or a dilated pelvis of a dynamic or mechanical nature may cause elongation and compression of the blood vessels. Likewise compression of the vascular pedicle may be caused by extrarenal and intrarenal neoplasms or metastatic nodules in the juxta-aortic lymph nodes.



C. *Congenital Polycystic Disease of the Kidney*.—The association of hypertension with polycystic disease of the kidneys is now well known to clinicians and urologists. Braasch was the first to call attention to the frequent occurrence of hypertension in this condition in 1916. Since then other writers, including Bell and Clawson, Braasch and Schacht, Hausman, Fishberg, Hawthorne and Rauscher, Albrittain and Cornbrooks, and Fahr, have commented on the frequency of persistent hypertension in these cases.

A review of the literature disclosed the fact that the opinion of Bell and Clawson, namely, persistent hypertension is not a frequent concomitant of congenital polycystic disease, is often quoted but rarely substantiated. To a nonbiased observer, it appears that their contention was based on insufficient data; i.e., the presence of a normal blood pressure in 4 of 8 cases of polycystic disease in which blood pressure determinations were made and the occurrence of cardiac hypertrophy in only 1 case.

Braasch and Schacht have presented very interesting statistics on the incidence of hypertension in polycystic disease. In a series of 190 patients whose average age was 43 years the systolic blood pressure exceeded 145 mm. of Hg in 61 per cent of the cases, and the diastolic pressure was more than 90 mm. of Hg in 55 per cent, and more than 95 mm. in 47 per cent. Elevated systolic blood pressures of 145 mm. or more were found in 71 per cent of the 71 patients reported dead of the disease. In a control group of the same age and sex, composed of patients suffering from chronic pyelonephritis, elevated blood pressure was found in 26 per cent. In this same group the incidence of hypertension among patients less than 50 years of age was 17 per cent as compared with 52 per cent of the patients in the same age group who were reported dead of polycystic disease.

Hawthorne and Rauscher found hypertension in 45 per cent of their 33 cases; Albrittain and Cornbrooks observed hypertension in more than 50 per cent of their 25 cases. Fahr noted hypertension in 4 of 6 cases. Fishberg maintained that the incidence of hypertension in this disease is between 65 and 75 per cent. Maher and Wosika observed 2 cases of polycystic diseases in their series of 101 cases of primary urinary tract pathology associated with hypertension.

Braasch and Schacht attributed the hypertension in polycystic disease to a generalized vascular disturbance as attested by the high incidence of retinal sclerosis and the frequent finding of obliterative changes in the small arteries and arterioles of the kidney. This contention is corroborated by the work of Himman and Morrison in 1924, and Ritter and Bachr in 1928 who studied the arterial tree of polycystic kidney by injections. The former investigators found that the circulatory changes in a polycystic kidney appear to be of a mechanical nature, involving chiefly the finer cortical vessels by displacement and compression. The larger vessels show but very little change. The circulation

of the entire kidney was of the fetal type which may be evidence of the embryonic origin of the disease. The latter investigators were the first to emphasize the decrease in the size of the small arteries and arterioles of the kidney and to point out the similarity between the clinical course of polycystic disease and that of malignant hypertension (arteriolar sclerosis) and chronic glomerular nephritis.

Ritter and Baehr described two distinct pathologic processes responsible for the changes in polycystic disease: (1) between the cysts areas of atrophic sclerosed parenchyma are found which are similar to the typical picture of a hydronephrotic contracted or a tubular contracted kidney and are the result of mechanical pressure; and (2) in the larger masses of parenchyma which are situated near the capsule of the kidney and proximal to the cysts, the pathologic changes consist of atrophic tubules, hyalinized glomeruli, dense connective tissue, and sclerotic changes in walls of the small arteries and arterioles and resemble the picture of a primary contracted kidney. In many instances the arteriolar and parenchymal changes, which may manifest themselves as early as the third decade and as late as the sixth decade, simulated those described by Fahr under the term of malignant sclerosis.

The clinical course of polycystic disease may closely resemble that of chronic glomerular nephritis and the true nature of the condition is frequently overlooked until an attack of hematuria, infection, pain, or a palpable mass directs the examiner's attention to the possibility of a nonnephritic lesion of the kidney. However, patients with polycystic disease experience greater longevity than do patients with nephritis despite the presence of serious impairment of renal function as demonstrated by marked retention of nitrogenous and nonnitrogenous products in the blood and consistently low excretion tests; i.e., phthalein, urea clearance, specific gravity, etc. The sequence of events is indistinguishable from that observed in patients with chronic nephritis or malignant sclerosis. Renal insufficiency, arterial hypertension, cardiac hypertrophy, and retinal sclerosis eventually ensue in most patients who live to adult life and azotemia or dry uremia usually terminates the clinical picture.

Bothe reported a case of hypertension associated with bilateral polycystic disease, more advanced on the left side, in an 8½-year-old girl. An acute pyelonephritis appeared to be the contributory factor in precipitating the hypertension which persisted after the infection subsided. The blood pressure rose from 128/86 to 145/115 during the four-month period of renal infection.

Braasch, Walters, and Hammer reported hypertension in a case of polycystic disease in which one kidney was functionless due to diffuse infection. Following nephrectomy the blood pressure returned to normal and remained so for one year. In another case, presenting a similar condition, the blood pressure was temporarily reduced following nephrectomy, but hypertension returned in a few months.

I have observed a case of hypertension (170/100) associated with early bilateral polycystic disease in a female, aged 32 years. The left kidney was the seat of a severe infection and was removed. During the period of convalescence the blood pressure fell to 118/78. Unfortunately the patient failed to return for further observation. Nephrectomy was performed in another case for a severe infection of one polycystic kidney which was unaccompanied by hypertension.

The following 2 cases, which are not included in Table III, illustrate hypertension associated with bilateral polycystic disease in which the more seriously damaged kidney has been treated palliatively by puncturing the cysts and establishing a nephrocutaneous fistula after the method of Goldstein. A temporary reduction in blood pressure level was obtained in both cases.

CASE 17.—(G. U., No. 4692.) L. R., white, female, 29 years of age, married, housewife, was admitted to the urologic ward of the Sinai Hospital on Jan. 26, 1932, complaining of severe headaches and pain in the lumbar regions and epigastrium. The family history was essentially negative. The patient had enjoyed good health until eight years previously when she sustained a cerebral concussion in an automobile accident. Following this accident, the patient began to complain of severe occipital and frontal headaches which have persisted to date. In 1928 she was told that the headaches were due to her tonsils which were removed without benefit. Subsequently she developed epigastric pain and discomfort after eating, dull persistent pain in the lumbar regions, accompanied by nausea but no vomiting. About one month before admission she developed urgency, diurnal and nocturnal frequency, and had a cystoscopic examination elsewhere following which she was told that she had a kidney ailment.

Examination revealed both kidneys to be palpable, the left being larger and more irregular in outline than the right. Ophthalmoscopic examination was negative. The urine had a specific gravity of 1.008, and was negative for albumin, for sugar, and microscopically. The blood urea was 28.76 mg. per cent. Phthalein test was 55 per cent for the first hour and 10 per cent for the second hour.

Cystoscopy and pyelography revealed a bilateral congenital polycystic disease of the kidney. A fractional phthalein showed the right kidney to excrete 12.5 per cent in fifteen minutes as compared to 20 per cent on the left. Because the right kidney appeared to be more extensively involved, it was decided to puncture the cysts in this kidney first. On Feb. 2, 1932, the right kidney was exposed through a lumbar incision under spinal anesthesia and many cysts were punctured (Rosving's operation). The patient made an uneventful recovery and was discharged from the hospital on Feb. 28, 1932. Prior to this operation, her blood pressure was 160/96; following operation it fell to 110/92.

The patient was followed in the outpatient department. Three years later she developed marked suprapubic discomfort and menstrual disturbances which were caused by a fibroid tumor of the uterus, and a hysterectomy was performed. In the past few months before readmission, the patient complained of occasional sticking pain in the left kidney region accompanied by a sensation of distention in the same area. She also complained of nausea, eructation, and constipation. In the last two weeks before readmission, her headaches returned in a more severe form. She had no urinary symptoms other than occasional nocturia. She also complained of dyspnea and occasional edema of her ankles and eyelids. She was readmitted to the hospital again on April 26, 1935.

At this time examination revealed the left kidney to be enlarged and tender. The surface of the left kidney was nodular and irregular and several large cystic masses could be easily mapped out. The right kidney was not palpable. Ophthalmoscopic examination disclosed narrowing of the arterioles, increased light streaking, and A-V nicking in both fundi but no hemorrhages or exudates. Cardiac hypertrophy was present. The blood pressure varied from 168/90 to 180/105. The urine had a specific gravity of 1.010 but otherwise was negative. The blood urea was 46.74 mg. per cent. The serum protein was 6.59 mg. per cent. Urea concentration tests revealed slight but definite renal impairment. The combined phthalein test was 28 per cent for the first hour and 15 per cent for the second hour. Fractional phthalein test at the time of cystoscopy showed an excretion of 3 per cent from the left kidney and 7 per cent from the right kidney in the first fifteen-minute collection and 2 per cent from the left kidney and 5 per cent from the right kidney in the second fifteen-minute collection.

On April 29, 1938, under avertin-ether anesthesia, a left nephrocutaneous fistula (Goldstein's operation) was established after aspirating and puncturing the cysts on the cortical surface. The patient made an uneventful recovery and was discharged from the hospital on June 12, 1938.

During her second stay in the hospital a daily blood pressure chart was kept. Following operation her blood pressure gradually declined to 130/70. Subsequent blood pressure determinations were taken in the outpatient department at intervals of three months. The last blood pressure was taken on Nov. 19, 1940, and was recorded as 144/82.

At the time of each operation, a piece of renal tissue was removed for histologic study. Extensive fibrosis with chronic inflammatory changes and hyalinization of the glomeruli tubules and smaller blood vessels were noted in several areas. In other areas, typical changes, i.e., dilatation of tubules and hypertrophy of glomeruli, were observed. The sclerotic changes in the walls of the smaller blood vessels were graded 1+.

CASE 18.—(G. U., No. 1868.) C. P. L., white, male, 45 years of age, married, merchant, was admitted to the Sinai Hospital on Feb. 3, 1936. His family history was negative. The patient had had an appendectomy in 1917. In November, 1932, he had had pneumonia complicated by a lung abscess, which drained spontaneously and healed in six months. In 1933 he developed an infection of the left kidney following the lung abscess. He passed blood and was cystoscoped elsewhere, but nothing further was done about this condition. In 1935 he had hematemesis, accompanied by epigastric pain and tarry stools. The patient was confined to a hospital for three weeks but has had no further recurrence of this trouble. In the past three years he has developed dyspnea on exertion, increasing fatigue, backache, occasional vertigo and tinnitus, blurred vision, vague muscle and bone pains, and anorexia.

Examination revealed an abdominal mass in both upper quadrants which were round, firm, and nodular. Voided specimen of urine had a specific gravity of 1.008 and a trace of albumin; microscopically, it showed an occasional white blood cell and several red blood cells. Cystoscopy and pyelography revealed congenital bilateral polycystic kidneys. The red blood count was 2,750,000, 38 per cent hemoglobin; white blood count was 7,000 with 70 per cent polynuclear neutrophils. Combined intravenous phthalein showed 4 per cent for the first half-hour; 6 per cent the second half hour; 1 per cent the third half-hour; and 2 per cent the fourth half hour. Blood creatinine was 5.2 mg. per cent; blood urea, 71 mg. per cent.

On Feb. 9, 1936, the left kidney was exposed and numerous cortical cysts were punctured and a nephrocutaneous fistula (Goldstein's operation) was established. The postoperative course was complicated by bronchopneumonia shortly after the operation. The patient was discharged on March 25, 1936. During the latter part of his stay in the hospital, there was a decided improvement in his general condition. The blood urea fell to 60 mg. per cent and the blood pressure, which on admission was 200/118, fell to 140/96. However, prior to discharge, his blood pressure gradually increased to 180/100. Following his discharge, he returned to his home in a neighboring state, but his general condition became progressively worse and signs of severe renal insufficiency developed and he died on Apr. 16, 1936.

A piece of renal tissue was removed at the time of operation for histologic study and revealed extensive fibrotic changes in the interstitial tissue between the cyst walls. There were relatively few blood vessels seen in the microscopic sections but the degree of vascular changes in these vessels was rather marked (grade 3+).

### DIAGNOSIS

Hitherto the urologist and often the internist have assumed a rather casual attitude toward hypertension, a symptom complex which is so vital in its relation to the kidneys and yet so devastating in its possible effects on the mechanism of the body as a whole. With the development of cystoscopic instruments, roentgenographic procedures, and laboratory tests of great precision and immeasurable diagnostic and prognostic value, the internist has gained a more thorough recognition of the immense importance of lesions of the urinary tract in hypertension and the urologist has acquired the necessary confidence to undertake the difficult task of treating such cases.

A complete and accurate diagnosis in every case of hypertension depends upon a careful analysis and correlation of all diagnostic means at our disposal. A comprehensive study of the genitourinary tract appears to be one of the most important diagnostic aids available. Its diagnostic value is greatly enhanced when one considers the frequent occurrence of urologic lesions in hypertensive patients as indicated in the clinical statistics of Maher and Wosika, Schroeder and Steele, Williams and Harrison, and others. In establishing the correct diagnosis of an urologic disease, the urologist must be on guard and not overlook an accompanying chronic nephritis or secondary arteriolar changes in the kidneys whose presence can be detected only by skillful utilization of various renal functional tests. The latter lesions, if neglected or overlooked, may exert considerable influence upon the clinical course of the urologic disease or the hypertension and occasionally leads to disastrous results during the course of an apparently innocuous therapeutic regime or following a well-performed operation. The urologist must also be cognizant of the tendency of the Bright's disease to mimic or be confused with other lesions of the urinary tract.

A careful and complete urologic study entails the utilization of the following diagnostic measures:

1. An accurate history
2. Thorough physical examination including
  - A. Blood pressure determination
  - B. Ophthalmoscopic examination
  - C. Special cardiac studies (i.e., electrocardiogram, teleroentgenogram)
3. Complete urinalysis
4. Laboratory tests
  - A. Complete blood chemistry (i.e., urea N., N.P.N., creatinine, serum sulfate)
  - B. Fractional phenolsulfonephthalein test
  - C. Special renal functional tests (i.e., urine concentration, urea clearance, inulin clearance, and diodrast clearance)
5. Roentgenographic studies
  - A. Plain film of the genitourinary tract
  - B. Intravenous urography
  - C. Retrograde pyelography
  - D. Perirenal insufflation
6. Cystoscopic study
  - A. Careful inspection of the lower urinary tract
  - B. Ureteral catheterization with collection of urine from each kidney for microscopic, chemical, and bacteriologic study
  - C. Differential functional tests (phthalein, indigo, carmine)
  - D. Bilateral retrograde pyelograms

A brief discussion of the pertinent features of each diagnostic method is herewith presented.

*History.*—An accurate history obtained from the patient or his family is an invaluable aid in the diagnosis and treatment of cases of hypertension associated with unilateral or bilateral diseases of the kidneys. Careful questioning will often reveal an antecedent infection or disease of the genitourinary tract whose effects or sequelae may have a direct etiologic relation to the hypertension. Attention must be directed not only to symptoms referable to the urinary tract but also to symptoms of other systems (i.e., cardiovascular) or organs (i.e., eyes) which may have a bearing on the problem at hand.

*Physical Examination.*—Having obtained a complete history, the next step is a thorough physical examination which should not be limited to the abdomen, genitals, and rectum but should cover the entire body. The general appearance of the patient should be carefully noted, as the keen observer can often discern some telltale signs of a constitutional disease or a specific organic lesion. Signs of renal insufficiency can often be detected. The urologist should not hesitate to avail himself of the services of an internist when evidence of cardiac pathology is found. Electrocardiogram and teleroentgenogram serve as useful adjuncts to the usual auscultatory examination and may be of inestimable value in determining the extent of the cardiac damage and the operability of the patient from a cardiac point of view. The urologist should familiarize himself with the use of the ophthalmoscope, for the presence or absence of vascular, inflammatory, or hemorrhagic changes in the fundi may prove to be of great assistance in differentiating between chronic

nephritis, nephrosclerosis, and chronic pyelonephritis. Changes in the caliber of the retinal vessels resulting from arteriolar disease, secondary to chronic pyelonephritis or a generalized disease process, may serve as one of the determining factors in the selection of cases of hypertension with unilateral renal disease suitable for nephrectomy.

*Blood Pressure.*—The routine determination of blood pressure is an essential part of every urologic examination. Urologists and internists alike are guilty of placing too much reliance on a single blood pressure reading obtained at the time of the initial examination. In view of the variability of the blood pressure in the same patient at different times, it is imperative that a blood pressure reading be taken not only at the start of the initial examination when the patient is nervous and apprehensive but also at, or near, the end of the examination, preferably prior to instrumentation, when the patient is in a more comfortable mental and physical state.

Blood pressure reading should be repeated at each subsequent office visit. When urologic patients suffering from renal calculi or infections are hospitalized, it is advisable to take blood pressure readings at least twice a day (in the morning and afternoon) for several days in order to rule out an associated hypertension. King and Keith stressed the advisability of taking blood pressure readings four times daily in urologic patients during the period of observation in order to detect the fluctuating type or paroxysmal type of hypertension. By this method variations due to nervous responses can easily be ruled out in patients suspected of having hypertension associated with unilateral or bilateral renal diseases, and the paroxysmal type of hypertension may be easily recognized in patients with adrenal medullary tumors. Following urologic operations, blood pressure readings should be taken daily. After discharge from the hospital, blood pressure should be taken at weekly intervals for the first few months, and later at monthly intervals.

There is no unanimity of opinion concerning the range of normal blood pressure. Robinson and Bruce made a detailed statistical study of the blood pressure in large groups of persons and concluded that the normal range of systolic blood pressure is between 90 and 120 mm. Hg and of diastolic pressure, between 60 and 80 mm. These figures are decidedly lower than those of other investigators. It is generally recognized that in normal children the blood pressure is lower than in adults and increases with age until at puberty it approaches the level of the adult.

Hines and his co-workers in the Mayo Clinic have made excellent intensive studies of the so-called normal blood pressure, its variations and its responses to the various tests. Hines recently studied the incidence of subsequent hypertension as correlated with the first reading of blood pressure which represented in most incidences the responses to nervous stress. It was found that excessive variations and excessive responses to the usual stimulation tests were indications of evidence of a possible

prehypertensive state. Patients whose blood pressure was not elevated as the result of nervous stress to more than 140 mm. systolic (or 85 mm. diastolic) are unlikely to develop hypertension subsequently; whereas, if the blood pressure under similar circumstances was less than 120 mm. systolic and 70 mm. diastolic, the patient was almost certain not to develop subsequent hypertension in the future. Conversely even transient elevation of the systolic and diastolic blood pressures into the upper range of normal are prognostic of probable subsequent hypertension. It was emphasized that elevation of the systolic blood pressure alone is not an indication of subsequent hypertension, which was more likely to occur when the diastolic pressure was elevated above the critical level of 85 mm. Hines recently maintained that heredity often determined whether or not a patient will develop hypertension as a result of renal disease.

Hines and Brown have shown by means of the "cold pressor test" that hypertensive patients show a greater response than do normal patients. The test was performed on a group of hypertensive children who were normal at the time of examination and revealed a positive response in a larger number of cases than in a similar group of nonhypertensive children. The cold pressor test consists of estimation of blood pressure immediately and at five-minute intervals, following the immersion of the hands or feet in cold water (4° C.) for a period of one minute.

Hardgrove, Roth, and Brown demonstrated a similar type of response with the inhalation of CO<sub>2</sub> and noted further that the responses were greater in the earlier cases of hypertension than in the advanced group.

#### LABORATORY TESTS

Laboratory studies of urine and blood are valuable aids in the diagnosis of urologic diseases. Unfortunately, there is no single laboratory test which affords a true evaluation of the renal function in every case. An accurate and complete estimation of renal function can be based only on the correlation of the findings of several different tests.

URINE EXAMINATION.—Urine examination must ever remain one of the most important steps in an urologic study, for much information can be obtained by a careful routine examination of the urine, preferably a catheterized specimen. As a rule, the determination of the specific gravity of a single voided or catheterized specimen is not of any great diagnostic value, but occasionally a low specific gravity may suggest the presence of polycystic disease or chronic nephritis. Hydrogen-ion concentration studies may provide valuable information from a therapeutic standpoint in the case of renal calculi and infections. Careful examination for albumin should be performed in every case in view of its significance in the early phases of renal pathology. Microscopic study of the centrifugalized urinary sediment is unquestionably a most important step in the examination of the urine, as the presence of ab-



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i.e., cardiac diseases, nervous diseases, abnormal metabolism, etc. Nevertheless, the functioning capacity of the kidney is a far more accurate index of the severity, course, and prognosis of renal disease than the degree of hypertension, hematuria, albuminuria, uremia, edema, etc. Unfortunately most of these tests necessitate quantitative chemical determinations which require special laboratories. Two tests of renal function are available to the urologist, internist, and general practitioner which can be performed with very little equipment and in a short time. Every urologist and clinician is fully acquainted with the use of the phenolsulfonephthalein test as a quantitative and qualitative measure of renal function, but few are cognizant of the fact that phenolsulfonephthalein is almost entirely excreted by the tubules with only 6 per cent excreted by the glomeruli, and that 50 to 70 per cent of the tubular epithelium must be damaged before an appreciable reduction in the total excretion occurs. The value of the test is limited by the presence of a complete or partial obstruction of the ureter, whereby tubular secretion is temporarily suppressed by back pressure or by the difficulty of collecting the urine trapped above the obstruction. The advantage of the test lies in the ability to determine accurately the rate of excretion over a two-hour period by noting the appearance time and estimating the amount of dye in the specimens collected every fifteen minutes, starting from the time of injection of the dye.

Shaw showed that the normal curve of elimination of phenolsulfonephthalein is characterized by an average output of 40 per cent during the first fifteen-minute period, 17 per cent during the second, 8 per cent during the third, 4 per cent during the fourth, and a gradual decrease to 0.5 per cent during the eighth period. Since the maximum excretion occurs in the first half-hour, collections of urine made at half-hour intervals will suffice for all practical purposes. The usual hour collections in vogue are impractical. All collections are dated from the time of administration of the drug rather than from the time of appearance of the drug in the urine. A record of the findings plotted in the form of a graph should be kept for future references and comparison. In the presence of vesical neck obstruction, it is essential that the bladder be emptied completely by catheterization or that an indwelling catheter be employed during the entire two-hour period. One cubic centimeter of the drug should be injected intravenously.

In a differential phthalein, which is performed with the catheter in each ureter, it is important to determine the time of the appearance of the drug in the urine, which is normally three to seven minutes. A large caliber Garceau ureteral catheter should be used to prevent leakage of the dye around the catheter. In differential phthalein, collections are made simultaneously from both kidneys during the same interval of time; i.e., preferably fifteen-minute and one-hour intervals; the starting point for the collections is the time that the dye is excreted from either side.

normal urinary constituents, i.e., pus cells, casts, erythrocytes, bacteria, etc., is confirmatory evidence of renal damage. Erythrocytes are not ordinarily detected in the urine until the number exceeds 5,000 cells per cubic centimeter of urine. The extreme sensitivity of the orthotolidine test warrants its use in every case in which erythrocytes are found in the urine; a 1+ test is obtained when the concentration is between 1,300 and 1,500 erythrocytes per cubic centimeter of urine; a 2+ between 4,000 and 7,000, and a 3+ between 5,000 and 20,000.

**BLOOD CHEMISTRY.**—The chemical constituents of the blood are maintained in equilibrium by delicate adjustments of the filtration and secretion through the glomeruli and tubules. In kidney diseases this mechanism is easily disturbed with resultant changes in the blood chemistry. However, in the past too much reliance has been placed on the estimation of blood urea nitrogen, nonprotein nitrogen, and creatinine as tests of renal function. Recent studies have shown that a normal blood urea and nonprotein nitrogen may exist even when extensive renal damage has occurred, and that the values of these nitrogen serum elements show an appreciable increase only after 50 per cent or more of kidney tissue is destroyed. The blood urea nitrogen concentration may be considerably influenced by extrarenal conditions; i.e., dehydration, high protein diet, hypochloremia, alkalosis, hypotension, etc. Furthermore the increased blood urea and nonprotein nitrogen merely serve to indicate the inefficiency of the kidney to excrete protein waste products and are not a true indication of renal impairment. Mosenthal advocated the use of the urea ratio; i.e., the relationship between blood urea nitrogen and nonprotein nitrogen as a measure of renal insufficiency.

Recently Wakefield, Powers, and Keith demonstrated that serum sulfate estimation is a more valuable index of renal function than either the urea nitrogen, nonprotein nitrogen, or creatinine. They found that the upper limit of normal serum sulfate concentration is 0.5 mg. per cent. In cases of renal insufficiency, there is a parallel increase in the blood urea and serum sulfate. Lazarus has employed this test to great advantage in the appraisal of nephritic states in urologic patients and maintained that an increased urea nitrogen concentration in the presence of a normal serum sulfate is more indicative of dehydration than renal pathology. The urea nitrogen concentration may be disregarded when the serum sulfate concentration is within normal limits.

**RENAL FUNCTIONAL TESTS.**—The importance of measuring the renal functional capacity in health and disease does not require emphasis. These tests indicate the functional capacity not only of the kidney but of the whole body. Renal functioning tests are interpreted the best when correlated or supplemented by other available clinical and pathologic findings. Renal functional tests merely indicate the presence of an impairment in renal function but do not permit differentiation of primary renal disease from renal lesions secondary to intrinsic or extrinsic changes in the genitourinary tract and constitutional changes;

renal damage, the specific gravity of the urine may become fixed at a low level, and the urea clearance test then becomes the only indicator of the progressive changes in the kidney lesion. A low urea clearance is significant of renal damage, except when urine volume is less than 20 c.c. per hour. One disadvantage of the urea clearance test is that it requires two hours to carry through.

Smith and his associates have made important physiologic contributions to the knowledge of glomerular filtration rate, total mass of functioning renal tissue (tubular excretory mass), and rate of blood flow to this. They utilized clearance methods based on the capacity of renal tubules to remove certain foreign substances from the blood and excrete them into the urine, independent of glomerular activity. The desired blood levels of from 100 to 150 mg. per 100 c.c. of inulin and from 0.5 to 5 mg. per 100 c.c. of diodrast were maintained by means of slow intravenous priming and sustaining solutions of inulin and diodrast in 1 per cent saline solution introduced simultaneously. From 1,000 to 1,500 c.c. of water are taken orally before each test and not more than 200 c.c. of water given during the procedure. They showed that phenol red, diodrast, and hippuran are excreted by a common cellular mechanism in the tubules and that the tubular excretory activity is limited in that there is a maximal rate of excretion for each substance. They pointed out that no significant quantity of each of the three substances is stored in the renal tubule.

They found that the clearance of inulin and phenol red in normal men is quite constant. The minimal renal plasma flow, as measured by diodrast clearance, has an average value of 820 c.c. per 1.73 sq. m. surface area per minute which corresponds to a minimal whole blood flow of 1,384 c.c.

Diodrast clearance approaches closely enough a complete clearance to be considered identical with renal plasma flow. A study of thirty-four observations in 15 normal subjects indicated the effective renal blood flow ranging from 1,050 to 1,580 c.c. (average 1,339 c.c.) or 595 to 916 c.c. (average 772 c.c.) of plasma per 1.73 sq. m. per minute. The glomerular filtration fraction ranged from 15.3 to 21.8 per cent (average, 17.7 per cent). The glomerular filtrate rate is measured by inulin clearance (the normal inulin clearance varied from 113 to 137 c.c. per minute with an average of 122) and the filtration fraction (i.e., the apparent fraction of plasma cleared through the glomeruli) is obtained directly by inulin diodrast clearance ratio.

ROENTGENOGRAPHY.—There are several roentgenographic procedures available for the study of urologic patients suffering from, or suspected of having, hypertension: viz., (a) plain roentgenogram of the kidney, ureteral and bladder areas; (b) intravenous urography; (c) retrograde pyelography; and (d) perirenal insufflation of air. Each procedure has its indications and limitations which must be thoroughly understood if the procedure is best to serve the patient as well as the physician.

Indigo carmine is not quite as accurate as phenolsulfonephthalein, inasmuch as not more than 25 per cent of this dye is excreted by the kidneys. However, this dye is excreted more rapidly than phenolsulfonephthalein or methylene blue and its chief advantage is that it provides a rapid means of estimating the differential function of each kidney, of localizing the ureter, and of determining the presence of functioning renal tissue, especially in congenital anomalies and pathologic conditions of the kidney.

**URINE CONCENTRATION.**—The urine concentration test as described by Lashmet and Newburgh and modified by Fishberg is a very simple and yet one of the most delicate tests for renal function. This test demonstrates renal impairment in its early compensating stages. A brief outline of the test is as follows:

1. At 6:00 P.M. on evening before test high protein meal with not more than 200 c.c. of water is taken.
2. No fluid or food is taken thereafter until test period is over.
3. All urine voided between 6:00 P.M. that evening and 8:00 A.M. next morning is discarded.
4. Specimen of urine is collected at 8:00 A.M., 9:00 A.M., and 10:00 A.M. in separate bottles and specific gravity of each is determined.

Normally the specific gravity of at least one specimen will exceed 1.025. Renal damage is shown when the specific gravity is below that level. A specific gravity below 1.020 shows considerable damage. The test is not reliable in patients with loosely held edema, associated with congestive heart failure and occasionally in nephrotic syndrome.

**Blood Urea Clearance Test.**—The accuracy of the blood urea clearance test, as described by van Slyke and Cope, depends to a great extent on measuring the urea secreted in the urine during an exact interval of time. It is extremely important to obtain all urine formed by the kidney during the tests; consequently, catheterization of the bladder should be performed in cases of obstructive lesions of the vesical neck or urinary incontinence. The blood urea clearance test is less sensitive than the urea concentration test, for in many instances the urea excreting function of the kidneys becomes impaired after the concentrating ability of the kidney is diminished. The test determines the amount of blood that is cleared of urea per minute and its efficiency is dependent upon the passage of at least 2 c.c. of urine per minute, the so-called augmentation limit. The normal value (100 per cent urea clearance) is 54 to 75 c.c. of blood cleared per minute with an urinary excretion rate of 2 c.c. per minute. It is generally recognized that evidence of renal impairment is manifested only when the urea clearance falls below 70 per cent; a reading of 30 per cent or lower is of grave prognostic significance.

It is well established that the urea clearance and concentrating ability of the kidney in general parallel each other. In the cases of extensive

the result of the observations on the excretory urographic changes and has served as an efficient measure of the total renal plasma flow. However, the correct evaluation of this test of the renal functional capacity must be correlated with other tests only when all factors responsible for the excretion of urine are known.

Intravenous urography has several shortcomings and limitations which should be realized by the urologist, radiologist, and clinician in order to prevent the indiscriminate use of such an extensive and time-consuming diagnostic method. Experience has shown that excretion urography is of little or no value in the diagnosis of renal tuberculosis, neoplasms and polycystic disease. Incomplete and irregular filling defects in the outline of the kidney, pelvis, and ureter which may simulate tuberculosis or neoplastic lesions of the kidney are frequently seen in patients with normal kidneys and an incorrect evaluation of these changes may lead to serious consequences from a diagnostic and therapeutic standpoint. The method is practically useless from a diagnostic standpoint in patients with minor degrees of renal infection (pyelonephritis) or extensive nonfunctioning pyonephrosis by virtue of its failure to demonstrate any anatomical changes. Intravenous urography should never be substituted for cystoscopy in cases of pyuria or hematuria. It is well to bear in mind that the mobility or failure to visualize one or both kidneys by this method is not necessarily due to a permanent, partial, or total impairment of the affected kidney. The same factors, which may interfere with the proper execution of phenolsulfonephthalein and other excretion tests of renal function, may operate in excretion urography.

3. *Retrograde Pyelography.*—This method obviously entails cystoscopy and ureteral catheterization. The method is practically indispensable for the accurate localization and identification of upper urinary tract disease. In my opinion, the only contraindications to retrograde pyelography are: (a) patients who do not tolerate instrumentation (i.e., aged, infirm, severe cardiac patients, etc.) and (b) hopeless patients in whom surgical interference is not possible and further information is unnecessary. With the perfection of cystoscopic instruments, refinement in cystoscopic technique, and development of innocuous pyelographic media, urologists no longer hesitate to perform bilateral pyelography. As a result of these advancements, we are now able to establish the correct diagnosis in the vast majority of cases. Retrograde pyelography is the most accurate procedure at our disposal in the diagnosis of renal neoplasms, polycystic disease, renal tuberculosis, and renal and ureteral calculi. It is the only reliable method for the graphic demonstration of the extent of the changes produced in the kidney by infection and calculi. Incomplete filling defects are not as likely to occur with this method, and in doubtful cases complete distention of the pelvis can be assured by employing pyeloscopy prior to pyelography. One cannot emphasize too strongly the value of ureteropyelograms taken in the

The value of each urographic procedure is dependent to a great extent upon the accurate and skillful interpretation of the various urograms which comes only through long experience with the normal findings and a familiarity with the various deformities and changes characteristic of early or late pathologic conditions in the urinary tract. Every patient subjected to any of the above procedures must be properly prepared in order to obtain good clear pictures devoid of shadows of collections of gas which may obscure or distort the urinary tract.

1. *Plain Roentgenogram.*—A plain roentgenogram of the abdomen taking in both kidneys and ureters as well as the bladder and prostate is indicated as a routine diagnostic measure (a) in every patient suspected of having a urologic lesion, (b) in every case of essential hypertension, and (c) in patients with vague abdominal symptoms or indistinct masses. In this many asymptomatic or unsuspected cases of urinary lithiasis, tuberculosis (with calcification), and renal neoplasms (with calcification) will be recognized which previously were erroneously diagnosed as some lesion of the gastrointestinal tract; i.e., appendicitis, cholecystitis, cholelithiasis, diverticulitis, etc. A plain film may also reveal changes in the adjacent osseous strictures which may have a significant diagnostic bearing on the case; i.e., changes in outline and density of vertebrae associated with arthritic or metabolic diseases, the presence of metastases in the vertebrae, ribs, and pelvis from a neoplasm within the genitourinary tract, or congenital or acquired developmental defects in the vertebrae associated with neurogenic disturbances in the urinary tract.

Great care must be exercised in differentiating calcified shadows overlying the kidney, ureter, bladder, and prostate in the absence of a complete urologic study, for not infrequently gallstones, calcified mesenteric lymph nodes, phleboliths, and papillomas are confused with or considered as evidence of renal, ureteral, or vesical calculi. The diagnosis is further complicated by the fact that the subjective findings associated with these extraurinary lesions may often simulate urologic lesions. It may be extremely difficult to interpret correctly the outlines of intraperitoneal and retroperitoneal tumors as distinguished from the normal or enlarged kidney or vice versa. In all such doubtful cases, an accurate diagnosis can be established only by resorting to other urologic diagnostic methods.

2. *Intravenous Urography.*—Excretory urography is of great value as a routine procedure in every case of essential hypertension and in puzzling urologic cases presenting atypical or vague symptoms. It is particularly valuable in those cases in which cystoscopy is contraindicated or impossible for various reasons. It has proved to be the best and frequently the only method for the demonstration of congenital anomalies of kidneys and ureters. This method also provides an excellent means of studying the function and dynamics of the kidneys. The diodrast clearance test as described by Smith and his associates is

obstruction of both ureters by intrinsic lesions (i.e., stones, tumors, or strictures) or extrinsic lesions (i.e., infiltrations from uterine carcinoma) which are known to respond well to the institution of good urinary drainage by catheterization or appropriate surgical measures. Furthermore, urologists and clinicians must not overlook the fact that many cases of hypertension associated with unilateral or bilateral renal diseases exist in which reduction of arterial blood pressure cannot be accomplished by operation but in which relief from other distressing symptoms and general improvement may occur after operation. The symptomatic relief obtained after nephrectomy or nephrostomy in cases of large infected hydronephrosis or calculous pyonephrosis, even in the presence of a lesion in the opposite kidney, is too well known and too dramatic to justify withholding appropriate surgical treatment which may not have the least influence on the accompanying hypertension. Conservation of kidney substance remains today, as in the past, a consideration of fundamental importance whenever it can be effected with a reasonable degree of respect for the future comfort and safety of the patient.

Cases of hypertension associated with unilateral renal disease are occasionally encountered which fulfill the above criteria for surgical intervention but which either fail to respond to nephrectomy or are followed by a temporary or slight reduction in blood pressure with subsequent return to the preoperative level. Although an explanation of such untoward results is not always available or forthcoming, several possibilities suggest themselves: (1) the existence of a primary factor of extrarenal origin which has been overlooked; (2) the existence of arteriolar changes in the opposite kidney or elsewhere in the body which cannot be detected by our present diagnostic methods; and (3) hereditary hypertensive factor which has been suggested by Hines to explain why some patients develop hypertension as a result of a specific unilateral renal disease, and others do not, but also why some hypertensive patients fail to respond to nephrectomy.

Unfortunately, a certain amount of unwarranted enthusiasm has been engendered by the early reports of cases of hypertension associated with unilateral renal disease which were successfully treated by nephrectomy. One gains an entirely different outlook after analyzing the recent comprehensive reports of Schroeder and Fish and of Braasch, Walters, and Hammer which include a careful follow-up study of the blood pressure over long periods of time after operation. Their results have shown that nephrectomy is by no means a panacea and that its indiscriminate use is certain to be followed by the needless sacrifice of much valuable, though damaged, renal tissue and often with a disastrous result to the patient. In the treatment of hypertension associated with unilateral disease, it behooves the clinician and surgeon (1) to evaluate and correlate the clinical and urologic findings in order to select cases suitable to surgical treatment and (2) to weigh assiduously the relative



recumbent and upright positions and of an eight-minute retention film in the diagnosis of nephroptosis. Stereoscopic pyelograms are particularly helpful in the localization of renal calculi and in the diagnosis of renal neoplasms.

4. *Perirenal Insufflation*.—This method was introduced by Carelli in 1921 as a means of obtaining better contrast between the kidney and the surrounding tissue. In 1921 Quinby and in 1935 Cahill adopted the procedure for outlining the adrenals in cases in which these glands were suspected of hypertrophy or neoplasm. It has also been employed by numerous investigators in cases in which the adrenal gland was suspected of being the cause of paroxysmal hypertension. While this procedure is generally more useful in the diagnosis of adrenal enlargements than other methods, i.e., intraperitoneal air injections and intra-arterial injection of colloidal thorium oxide, it should not be adopted as a routine measure, as several cases of death from embolism have occurred following perirenal insufflation. The technique is simple and easily carried out in the x-ray room with a minimum amount of discomfort to the patient.

**CRITERIA FOR SURGICAL INTERVENTION.**—It is extremely difficult to determine exactly which type of case of hypertension and unilateral renal disease is suitable for operative treatment. The experience and results of other surgeons emphasize the fact that an intensive study of each case is essential in order to select cases amenable to this form of therapy.

As a result of their extensive clinical study and a limited but well-rounded surgical experience, Schroeder and Fish have proposed five criteria to aid in the selection of cases for surgical treatment. I am of the opinion that these criteria admirably fulfill the necessary clinical and surgical requirements and urge their adoption by every genito-urinary surgeon called upon to treat such cases:

1. The arterial hypertension must be of recent origin (arbitrarily placed at two years).
2. The renal lesion must be confined to one kidney and must have produced a diminution in the function of this kidney.
3. The combined renal function of both kidneys, as determined by urine concentration and urea clearance tests, must be within normal limits.
4. Retinitis should be absent and the changes in the retinal vessels should be minimal.

5. The arterial blood pressure must be persistently elevated.

It must be remembered that the above criteria are applicable only to the employment of nephrectomy in the treatment of cases of hypertension due to unilateral renal disease and must not be interpreted as excluding from appropriate surgical treatment the large group of urologic cases with hypertension resulting from bilateral renal disease secondary to obstruction in the upper or lower urinary tract. For example, these criteria are not intended to cover cases of prostatic enlargement or

TABLE I

RELATIVE INCIDENCE OF HYPERTENSION IN 167 CASES OF UNILATERAL RENAL DISEASE TREATED BY NEPHRECTOMY

UNILATERAL RENAL DISEASE	ALL CASES	HYPERTENSIVE CASES (SYSTOLIC B.P., 145 MM. OR MORE)	
		NO.	%
Neoplasm	24	3	12.5
Tuberculosis	15	3	20
Pyelonephritis			
A. Acute	9	1	11.1
B. Chronic	9	1	11.1
Stone			
A. With Infection	44	13	30.2
B. Without Infection	9	1	11.1
Hydronephrosis			
A. Uncomplicated	4	0	
B. Complicated	16	3	18.7
Pyonephrosis	21	3	14.2
Traumatic	3	0	
Miscellaneous	13		7.6
A. Polycystic	2	1	
B. Ectopic Kidney	3	0	
C. Solitary Cyst	2	0	
D. Perirenal Cyst	2	0	
E. Hypoplastic Kidney	3	0	
F. Horseshoe Kidney	1	0	
Total	167	29	17.3

In Table I, I have classified the various pathologic lesions encountered and have indicated the relative incidence of hypertension in each group. As was to be expected, the incidence of hypertension varied widely in the different renal diseases. The percentage was highest in cases of renal calculi accompanied by chronic pyelonephritis. In this group of 44 cases of renal calculi with chronic renal infection the pathologic diagnosis was chronic pyelonephritis in 33 cases and pyonephrosis in 11 cases. Hypertension was present in 10 cases of stone and chronic pyelonephritis and in 3 cases of calculous pyonephrosis. We were greatly impressed by the fact that hypertension occurred most frequently in patients with chronic renal infection; viz., chronic pyelonephritis with or without stone, pyonephrosis with tuberculosis. Our clinical and pathologic findings substantiate the observations of Braasch, Walters, and Hammer: i.e., (a) chronic renal infection, accompanied by extensive atrophic changes in the renal parenchyma and sclerotic changes in the smaller renal vessels, is an important factor in the development of hypertension; and (b) the other clinical features of chronic renal infection, i.e., severity, duration, impaired renal function, pyuria, and pyelographic changes, do not appear to exert any appreciable influence upon the development of hypertension. The one case of hypertension associated with renal calculus without accompanying renal infection occurred in a male, 64 years of age, who had hypertensive cardiovascular disease. In our experience acute renal infections are rarely accompanied by hypertension as evidenced by the fact that pre-

merits and efficacy of the various surgical procedures. It must be constantly borne in mind that nephrectomy is indicated only in carefully selected cases, as mentioned above, and is contraindicated in others. For example, nephrectomy offers no hope of reducing the blood pressure in cases of hypertension of extrarenal origin in which the presence of a unilateral renal disease bears no etiologic significance but merely represents a coincidental or accidental finding. Braasch, Walters, and Hammer have aptly summarized the contraindications to nephrectomy in cases of hypertension associated with unilateral renal disease. They maintained that nephrectomy should not be employed in the presence of (1) extensive bilateral renal disease, (2) extensive secondary degenerative changes in other organs, (3) advanced renal insufficiency, and (4) a serious unrelated but inoperable lesion elsewhere in the body.

#### SUMMARY OF PRESENT SERIES OF CASES

I have undertaken a review of 167 consecutive nephrectomies performed on the urologic service of the Sinai Hospital in the ten-year period Jan. 1, 1930, to Dec. 31, 1939, in order to determine (a) the relative incidence of hypertension in advanced unilateral renal disease, (b) the age and sex distribution, (c) the immediate and late effect of nephrectomy upon the hypertension in such cases, and (d) the correlation of the clinical findings and postoperative course of hypertension with renal parenchymal and vascular changes. I am cognizant of the limitations and dangers of drawing any definite conclusions from a small series of cases but present the following data in the hope that it will contribute in a small measure to the sum total of our knowledge of this subject.

*A. Relative Incidence of Hypertension in Unilateral Renal Diseases.*—In our clinic it has been the custom to consider a state of hypertension to exist in a given individual if the systolic blood pressure exceeded 145 mm. Hg and the diastolic pressure showed a corresponding increase usually above 90 mm. Hg. In this study I accepted the "mean" of all known preoperative blood pressure readings as the correct blood pressure of the patient whenever such data were available. However, in some instances we were forced to rely on a single blood pressure determination which was usually taken on the day before operation, i.e., several hours after admission to the hospital, and consequently the latter readings may be a few millimeters higher than normal due to the emotional stress and strain induced by the knowledge of an impending operation.

Hypertension was present prior to operation in 29 (17.3 per cent) of the 167 nephrectomized patients (Table I). This figure is slightly lower than that reported by Braasch, Walters, and Hammer, who observed hypertension in 315 (18.4 per cent) of 1,684 patients subjected to renal surgical procedures and in 195 (20 per cent) of a random group of 975 consecutive adult patients.

TABLE II

## AGE AND SEX DISTRIBUTION OF CASES

AGE	NEOPLASM		TUBERCULOSIS		PYELONEPHRITIS (ACUTE)		PYELONEPHRITIS (CHRONIC)		STONE (WITH INFECTION)		STONE (WITHOUT INFECTION)		HYDRONEPHROSIS (UNCOMPLICATED)		HYDRONEPHROSIS (COMPLICATED)		PYONEPHROSIS		TRAUMATIC		MISCELLANEOUS		TOTAL NO. CASES	AVERAGE AGE	SEX		AGE DISTRIBUTION OF HYPERTENSIVE CASES
	Y.	N.	Y.	N.	Y.	N.	Y.	N.	Y.	N.	Y.	N.	Y.	N.	Y.	N.	Y.	N.	Y.	N.	FEMALE	MALE					
1 to 9																							5	4	3	12	
10 to 19																							2	18	13	3	
20 to 29																							26	24.8	19	4	
30 to 39																							39	35.2	20	3	
40 to 49																							33	43.7	21	4	
50 to 59																							37	53	11	4	
60 to 69																							25	63.3	6	4	
Total	3	21	3	12	1	8	1	8	13	31	3	9	4	3	13	4	3	18	3	1	1	12	167		73	94	20

\*Y, hypertensive cases; N, nonhypertensive cases.

operative hypertension was present in only 1 of 9 cases of acute surgical infections of the kidney; i.e., acute pyelonephritis with or without perinephritic abscess and renal carbuncle. Furthermore, there is some doubt as to the exact etiologic factor responsible for the hypertension in this 1 case as the patient was a female 60 years of age, who had been treated for hypertension for several years but was admitted and operated upon for an acute pyelonephritis and perinephritic abscess.

It is difficult to attach any significance to the high incidence of hypertension in renal tuberculosis in our small series. However, it is interesting to note that 2 of the 3 patients with hypertension had been previously treated for pulmonary tuberculosis in sanatoriums and had clinical evidence of active tuberculous lesions in other organs at the time of nephrectomy.

The incidence of hypertension in cases of hydronephrosis complicated by renal infection, ureteral stricture, and peripelvic adhesions was rather striking. Two of the 3 cases were encountered in our youngest patients, aged 19 months and 8½ years, who had congenital valves of the posterior urethra with bilateral hydronephrosis and congenital ureterovesical stricture, respectively. The third patient was a male, 52 years of age, who had a large infected hydronephrosis due to a stricture at the ureteropelvic junction.

There were only 3 cases of hypertension associated with renal adenocarcinoma in our series of 24 cases. These occurred in men past 50 years of age; viz., 52, 62, and 63 years. One patient had a calculus in the renal pelvis in addition to the renal neoplasm. In our series of 24 cases, the neoplasm was of the hypernephroid type of adenocarcinoma, with the exception of 1 case of papillary carcinoma of the renal pelvis.

*B. Age and Sex Distribution.*—It is difficult to evaluate the influence of age as a factor in the development of hypertension in so small a series of cases, particularly since 105 patients were below the age of 50 years. In our study the factor of age was particularly significant in explaining the comparatively high incidence (12.5 per cent) of hypertension in the group of 24 neoplasms since 18 of these patients were over 50 years of age and the 3 hypertensive patients were in this age group. The age may be considered an important factor in explaining the high incidence of hypertension in association with chronic renal infection since 11 of 15 patients with renal tuberculosis were below the age of 40 years and 25 of 44 patients with stones accompanied by chronic pyelonephritis were below the age of 50 years. The youngest hypertensive patients were two boys, 19 months and 8½ years of age respectively, who had nephrectomies performed for infected hydronephroses. The oldest hypertensive patient was a male, 64 years of age, who had a kidney removed because of hematuria due to a renal calculus but also suffered from hypertensive cardiovascular disease.

PREOPERATIVE DIAGNOSIS	PATHOLOGIC DIAGNOSIS	DEGREE OF VASCULAR CHANGES	REMARKS
Hydronephrosis (L) Stricture at ureteropelvic junction (L) Rupture of kidney (L)	1. Hydronephrosis 2. Acute and chronic pyelonephritis	++	Slight permanent improvement in blood pressure; plastic operation on left renal pelvis 3 mo. previously
Chronic pyelonephritis (L) Solitary cyst (L)	1. Chronic pyelonephritis 2. Cortical abscesses 3. Solitary cyst	++++	Temporary improvement for 6 weeks followed by gradual elevation above preoperative level; died of cardiorenal insufficiency 4½ mo. after operation
Pyonephrosis (R)	1. Tuberculous pyonephrosis 2. Chronic pyelonephritis	++	Slight improvement in blood pressure; marked improvement in general health
Tuberculous kidney (R) Tuberculous ureter (R) Tuberculous bladder	1. Tuberculous kidney	+	Marked permanent improvement in blood pressure to date
Tuberculous pyonephrosis (R) Tuberculous epididymitis (R) Tuberculous orchitis (L)	1. Tuberculous kidney 2. Tuberculous orchitis	++	Marked permanent improvement in blood pressure to date (left orchidectomy 2 mo. previously)
1. Renal calculi (R) 2. Chronic pyelonephritis (R) 3. Stricture at ureteropelvic junction (R)	1. Chronic pyelonephritis 2. Kidney infarcts 3. Renal calculi	+	Slight improvement in blood pressure; marked improvement in general health
1. Calculous pyonephrosis (L)	1. Chronic pyelonephritis 2. Renal calculus	+	Slight improvement in blood pressure; marked improvement in general health
1. Chronic pyelonephritis (R) 2. Renal calculi (R)	1. Chronic pyelonephritis 2. Renal calculi 3. Kidney infarcts	++	Slight improvement in blood pressure; secondary ureterectomy 3 mo. later; marked improvement in general health
1. Calculous pyonephrosis (R)	1. Pyonephrosis 2. Renal calculi	++	Slight improvement in blood pressure; marked improvement in general health
1. Renal calculi (R) 2. Pyonephrosis (R)	1. Chronic pyelonephritis 2. Pyonephrosis 3. Renal calculi	++++	Slight temporary improvement in blood pressure followed by gradual return of preoperative level
1. Multilocular hydronephrosis (R)	1. Multilocular hydronephrosis 2. Chronic pyelonephritis	+	Slight improvement in blood pressure; marked improvement in general health (exploratory laparotomy 40 days previously)
1. Pyonephrosis (L)	1. Pyonephrosis 2. Chronic pyelonephritis	++	Slight improvement in blood pressure; marked improvement in general health
1. Pyonephrosis (R)	1. Pyonephrosis	++	Slight improvement in blood pressure; marked improvement in general health (right nephrolithotomy 3 mo. previously)
1. Hypernephroma (R)	1. Hypernephroma 2. Chronic pyelonephritis 3. Chronic nephritis	++	Slight improvement in blood pressure (died 5 yr. after operation of cerebral hemorrhage)
1. Hypernephroma (L)	1. Hypernephroma 2. Renal calculus	-	Slight improvement in blood pressure; slight improvement in general health
1. Hypernephroma (L)	1. Hypernephroma	+	Slight improvement in blood pressure (died 1 yr. after operation of cardiac failure)

TABLE

## SUMMARY OF 16 CASES OF

CASE NO.	NAME	AGE	SEX	DURATION OF HYPERTENSION	PREOPERATIVE OPHTHALMOSCOPIC FINDINGS	PREOPERATIVE RANGE OF BLOOD PRESSURE	POSTOPERATIVE RANGE OF BLOOD PRESSURE	NO. OF MONTHS OR YEARS FOLLOWED	LAST RECORDED BLOOD PRESSURE
1.	J. P.	52	M	3 yr.		200/100 210/110	166/ 96 170/100	152/108	3 yr.
2.	L. W. M.	50	M	5 mo. (?)	Markedly advanced hypertensive changes	220/116 228/124	140/ 98	260/140	3 mo.
3.	A. B.	36	F	1 yr.		160/ 90 168/ 98	140/ 90	140/ 90	2 yr.
4.	D. L.	21	F	1 yr.		148/ 86	120/ 80	120/ 80	4 yr.
5.	D. P.	24	M	1 yr.	Early hypertensive changes	144/ 92 150/ 96	122/ 78	120/ 78	2 yr.
6.	S. D.	48	F	3 yr.		188/100 210/110	124/ 60 138/ 70	158/ 92	13 mo.
7.	J. C.	49	M	2 yr.		166/ 84 174/ 92	140/ 80	132/ 80	3 yr.
8.	J. R.	52	M	2 yr.	Moderately advanced hypertensive changes	192/110 196/114	162/100 158/100	134/ 80 140/108	13 m
9.	R. C.	38	F	2 yr.	Normal	160/100 164/110	120/ 80	146/100	22 n
10.	R. G.	51	F	6 yr.	Markedly advanced hypertensive changes	220/120	140/ 90	245/135	2 ;
11.	J. B.	8½	M	2 yr. (?)		140/ 84 160/100	135/ 80	120/ 82	7½
12.	C. J.	56	M	3 yr.	Moderately advanced hypertensive changes	180/120 186/124	140/ 90 144/ 92	170/110	4
13.	M. K.	51	M	2 yr.		184/110 188/114	152/ 92	142/ 90	;
14.	W. T.	52	M	2 yr.		180/110 184/112	154/ 82	154/ 82	
15.	A. W.	62	M	2 yr. (?)		168/ 86	140/ 80	140/ 80	
16.	J. S.	63	M	3 yr.	Well-advanced hypertensive changes	220/110	162/ 88	162/ 88	

The failure to obtain a striking or prolonged reduction in blood pressure following this form of therapy in the latter two groups may be attributed to either one or both of the following reasons: (a) the removed kidney was not the sole etiologic factor responsible for the hypertension, or (b) hypertensive vascular changes were present in the opposite kidney or in other organs which were not discernible by our diagnostic measures but which had progressed to a permanently irreversible status and militated against a good result.

We feel that a guarded prognosis must be given in every case of hypertension in which the removal of a diseased kidney is contemplated in view of the fact that a complete relief of hypertension or a marked permanent reduction in postoperative blood pressure is obtained in comparatively few cases; whereas, a slight temporary or permanent reduction is to be expected in the majority of cases. However, we are convinced that complete relief of hypertension can be expected in carefully selected cases which fulfill the preoperative criteria proposed by Schroeder and Fish for the selection of cases suitable for nephrectomy.

*D. Correlation of Renal Parenchymal and Vascular Changes With the Preoperative Clinical Findings and Postoperative Blood Pressure.*—With the assistance of the hospital pathologist, Dr. T. Weinberg, a special study was made of gross and microscopic features of each operative specimen in the 16 follow-up cases. Particular emphasis was placed on the degree of acute or chronic inflammatory changes, parenchymal atrophy, and vascular changes in small renal arteries and arterioles in each specimen. As a result of this study, we had hoped to establish a relationship between the pathologic finding and the preoperative and postoperative hypertension but found we were confronted with a mass of data which appeared to be inconsistent and even contradictory in some instances. From this meager amount of information we have hesitated to draw any specific conclusions or to correlate the pathologic findings with the hypertension. Nevertheless, certain pertinent observations were made from this limited series which appear worthy of record.

Every kidney removed in the 16 follow-up cases showed, in addition to the primary pathologic lesion, varying degrees of acute and chronic inflammatory changes as well as vascular changes in the smaller renal arteries. We undertook to classify arbitrarily the degree of vascular change in each kidney from grade 1+ to grade 4+, bearing in mind that the degree of vascular damage, as indicated in a limited number of histologic sections from each kidney, does not always serve as a true index of the degree of renal ischemia present. In our experience the best results from the standpoint of reduction in blood pressure were obtained in cases (i.e., Cases 4, 5, and 11) which had the least amount of vascular damage and parenchymal atrophy. On the other hand, we have observed 3 cases (Cases 6, 9, and 15) in which the degree of vascular damage and parenchymal atrophy was considered as minimal or scant,



The sex distribution of the 167 cases is shown in Table II. The cases of hypertension associated with unilateral renal diseases were practically equally distributed between the two sexes; viz., 15 males and 14 females. Eleven of the 14 females with hypertension were between the ages of 20 and 50 years and belonged to the group of chronic renal infection; viz., 2 tuberculosis and 9 stone with chronic pyelonephritis. The relatively high incidence of hypertension in females with renal calculi associated with chronic pyelonephritis may be explained by the frequent occurrence of such lesions in women of the childbearing age. Each of our 9 patients gave an antecedent history of either pyelonephritis of pregnancy or renal calculi or infection developing soon after pregnancy was terminated.

*C. The Effect of Nephrectomy Upon Hypertension Associated With Unilateral Renal Disease.*—A follow-up study of the postoperative course of the blood pressure was made in 16 of the 29 cases with hypertension as shown in Table III. In analyzing our results we were greatly surprised to find so few cases obtained a complete relief or a prolonged reduction of the hypertension as compared to the early enthusiastic reports of remarkable cures of hypertension following nephrectomy. Our best results were obtained in a relatively small number of cases in whom (a) the hypertension and clinical signs and symptoms of renal diseases were of comparatively recent origin (i.e., two years or less), (b) little or no impairment of renal function had occurred, and (c) no hypertensive vascular changes were present in the opposite kidney or elsewhere in the body.

Our results may be summarized as follows: (1) In every instance the removal of the diseased kidney was followed by an immediate but temporary reduction of the blood pressure for periods varying from three weeks to four months. It is difficult to determine to what extent this temporary lowering of the blood pressure is due to physiologic rest and inactivity during the period of convalescence or to a change in the pathologic physiology of circulation resulting from the removal of one hypertensive factor; i.e., the diseased kidney. (2) A striking improvement in postoperative blood pressure, which was manifested by a marked permanent reduction lasting from two to seven years, was observed in only 3 cases (Cases 4, 5, and 11). (3) A slight improvement of a permanent nature was noted in 9 cases (Cases 1, 3, 6, 7, 8, 9, 13, 14, and 15). Despite the removal of one hypertensive factor, these patients must be considered as remaining actually or potentially hypertensive. (4) Little or no improvement was observed in four cases (Cases 2, 10, 12, and 16). These patients exhibited a temporary reduction in blood pressure after nephrectomy which was followed in several months or years by a gradual increase in blood pressure approaching or exceeding the preoperative level. In retrospect the clinical course of 2 patients (Cases 2 and 10) was strongly suggestive of "malignant" hypertension.

6. In some cases the blood pressure returned and remained at a normal level following nephrectomy which may be attributed to the fact that the unilateral renal disease was the primary factor responsible for the hypertension and that secondary arteriolar changes in the opposite kidney or in other parts of the body were absent or had not progressed to an irreversible degree.

7. In other cases, the end results from the standpoint of reduction in arterial blood pressure were not as striking following nephrectomy; i.e., the immediate effect was a transitory lowering of the blood pressure for a few weeks or months followed by a gradual return to the pre-operative level.

8. In a small number of cases, notwithstanding the fact that a definite causal relation between the hypertension and the unilateral renal disease could be established, neither an immediate nor late reduction in arterial pressure occurred after nephrectomy. This may be explained on the basis that either the unilateral diseased kidney was not the sole etiologic factor or the disease process had been present over a long period of time and had caused secondary arterial changes in its mate or elsewhere in the body which were responsible for the persistent hypertension.

9. It is important that an adequate period of time, at least one year, should elapse following operation before one attempts to evaluate the permanency and extent of the reduction in arterial blood pressure.

10. In view of the uncertain end results and insufficient period of observation in the reported cases, there appears to be no justification for considering nephrectomy as a panacea for the cure of hypertension in every case of chronic unilateral disease of the kidney.

11. Every case of hypertension associated with unilateral renal disease should be subjected to a careful and complete urologic study in order to select those cases suitable to operation and to prevent the needless sacrifice of renal tissue in those patients who can ill afford to lose same.

12. Every clinician and urologist should recognize the limitations and contraindications to nephrectomy in the treatment of hypertension associated with unilateral renal disease. It must be remembered that nephrectomy may be fatal in cases of hypertension of long duration or those whose clinical course is suggestive of the so-called "malignant hypertension."

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but following nephrectomy only a slight improvement in the blood pressure of a temporary or permanent nature resulted. We have also encountered several patients, particularly in the group of renal calculi accompanied by chronic pyelonephritis and a pyonephrosis, who did not have hypertension but in whom extensive parenchymal and vascular changes were found. The latter findings serve as confirmatory evidence of the fact that unilateral renal diseases accompanied by vascular changes are not the only etiologic factors responsible for the development of hypertension.

Extensive vascular and parenchymal changes (grade 4+) were noted in 2 patients (Cases 2 and 10), who had the most severe degree of pre-operative hypertension and obtained poor results following nephrectomy. Undoubtedly the recurrence of the elevated blood pressure in these cases after the temporary reduction incidental to the removal of the affected kidney may be attributed to the presence in opposite kidney and other organs of hypertensive vascular changes of an irreversible nature.

#### CONCLUSIONS

It is quite obvious that any clinical deductions, which are based on the analysis of the small number of cases of hypertension and unilateral renal disease reported in the literature and a personal experience limited to 16 cases, must necessarily be tentative and guarded. When the knowledge gained from such clinical surveys is supplemented by the observations and results of animal experimentation and pathologic study of autopsy material, there appears to be sufficient evidence to warrant the following conclusions:

1. The diagnosis of "essential hypertension" should be made with great reservations. Every patient with hypertension of unknown etiology should be subjected to a comprehensive study of the entire body, including a complete urologic study. The value of the latter type of investigation is emphasized by the frequent occurrence of urologic lesions in hypertensive cases as indicated in recent clinical and statistical reports.

2. The presence of a urologic lesion in a hypertensive patient must be carefully evaluated from an etiologic standpoint for not infrequently such a lesion is coincidental and bears little causal relationship but may influence considerably the clinical course of the hypertension.

3. There is a definite causal relation between hypertension and certain specific types of advanced unilateral renal disease; i.e., chronic pyelonephritis, hydronephrosis, ptosis, tuberculosis, Wilms' tumor, etc.

4. The same type of lesion occurs in many patients without the slightest elevation in blood pressure.

5. In certain selected cases appropriate surgical procedures, designed to remove or correct the unilateral renal lesion, have resulted in a considerable improvement in blood pressure findings.

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# Review of Recent Meetings

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## THE SOCIETY OF UNIVERSITY SURGEONS

ALEXANDER BRUNSCHWIG, M.D., CHICAGO, ILL.

THE third annual meeting of the Society of University Surgeons was held at the Barnes Hospital, Washington University School of Medicine, St. Louis, Mo., Feb. 14 and 15, 1941.

The meeting was opened by **Evarts A. Graham** who gave a clinic on the advances of thoracic surgery during the past two decades.

Most of the papers presented at this meeting are to be found in this issue of **SURGERY**. Brief abstracts of other papers presented at that meeting are summarized herewith.

**Max Taffel and Sam C. Harvey, Yale University: Effect of Sulfanilamide on Wound Healing.**—Sulfanilamide did not appear to retard or inhibit the healing of stomach wounds in rats. Curves of healing of these wounds as measured by their tensile strength were practically identical in the control and experimental groups. Histologic studies of the wounds at each time interval revealed no striking differences in the two groups. The drug was administered orally.

**Max Taffel and W. J. German, Yale University: The Effect of the Local Application of Various Sulfonamides Upon the Brain.**—These experiments are still in progress and this report is a preliminary one. Sulfanilamide, sulfapyridine, sulfathiazole, and sulfanilylguanidine were applied respectively to the brains of monkeys, and histologic examinations made of the sites of application after four, ten, and twenty days. In the first group of animals the drug was placed upon the intact pia-arachnoid. In the second group a portion of the cortex was scooped out and the drug placed upon the exposed raw cortical surface. The local tissue reaction was approximately the same for all the drugs. It consisted essentially of a mild foreign body reaction characterized by the presence of variable amounts of multinucleated giant cells which had enveloped crystals of the drug. The studies thus far show that the cerebral tissue does not appear to be appreciably altered by the presence of the drug. Special stains are being investigated to verify this finding.

**Warfield M. Firor, Johns Hopkins University: The Use of Bactericidal Agents in the Colon.**—Preliminary evidence was obtained to show that sulfanilylguanidine markedly inhibited bacterial growth in the colon. The implications for colon surgery were discussed.

**Joseph W. Beard, Duke University: Purification and Properties of the Equine Encephalomyelitis Virus.**—Crude extracts of chick embryos diseased with equine encephalomyelitis treated with formalin lose all infectivity and subsequently possess the capacity to immunize against the active virus. The nature of the immunizing material has been the subject of much study. Information in this respect has been afforded by formalization of the purified virus under controlled



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## Book Review

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**Entre Cirujanos y Hospitales (Among Surgeons and Hospitals)** By Dr. José Castro Villagrana, Mexico City, 1940, published in Spanish by the author. 1 vol, pp 202.

At this moment when the terms Pan Americanism, Pan American Union, Pan American Congress, etc, are heard everywhere as the expression of the growing importance of Latin American cooperation in harmonizing the common interests of the democracies of the Western Hemisphere for their mutual good in every sphere of their international relations, messages of good will and professional fraternalism are particularly welcome. Such is the message conveyed by Dr. José Castro Villagrana in his remarkable memoir of travel in American and Europe, entitled *Among Surgeons and Hospitals* which is now before us.

It is surprising that despite the fact that Mexico has become in recent years the magnetic center of attraction to the American tourist, and despite the enormous literature that is piling up on every phase of Mexican history and Mexican life, there is so little known or written on the medical institutions and medical activities of our neighboring republic by the profession on this side of the Rio Grande. For this reason the opinions and observations of a capable and thoroughly representative observer of our own institutions, even though limited to the surgical sphere, are well worthy of extended notice.

This is a remarkably interesting narrative of travel by a Mexican surgeon gifted with an artistic temperament and a fine scholarly capacity for describing and reflecting on what he sees and hears. Despite the total exclusion of all official titles, the author of this memoir (who could display them in profusion) is too well known as one of the outstanding and most progressive surgeons of the younger generation in Mexico City to require them.

As professor of surgery in the faculty of the medical school, director and chief surgeon of the Juarez Hospital, one of the largest (2,000 beds) and one of the oldest in its historical foundations, Dr. Castro Villagrana has been largely instrumental in introducing many innovations in surgical education and in rebuilding and completely modernizing an obsolete old hospital, formerly the San Pablo, which traced its origin to a sixteenth century (1569) Franciscan church and school for Indians, serving later as barracks and military hospital until 1872, when it became the Juarez Hospital.

Besides the epochal architectural and administrative transformation that the Juarez Hospital has undergone during the period of Dr. Castro Villagrana's incumbency, he has been a pioneer and tireless leader in the most recent movements that tend to unify the surgeons of his country in a constant effort to increase the efficiency of their hospitals as community centers for surgical relief and the training of surgeons. All of this is attested by his initiation and participation in the founding of the important Surgical Society of Juarez, in the National Association and Assembly of Mexican Surgeons, the National Hospital Association, the Mexican Society of Anesthetists, the Training School for Nurses, the establishment and development of social service in hospitals and in the organizations of the student body that tend to fit them for the higher responsibilities of the medical profession.

conditions. The product of such procedure has been practically indistinguishable by means of the analytical ultracentrifuge from the untreated virus, indicating that the essential immunizing component is comprised in the main of an inactive formalin product of the virus. Under proper conditions, an identical material can be obtained from the crude vaccines.

**Henry Poer, Emory University: Lymphosarcoma of the Duodenum. Case Reports.**

**Alexander Brunschwig and Richard A. Rasmussen, University of Chicago: Benign Neoplasia of the Stomach and Diet.**—Rats on various types of deficient diet develop ulceropapillomas and papillomas of the rumen and true stomach. This is a manifestation of a certain degree of malnutrition, the latter being of no specific type.

**I. Ridgeway Trimble, Johns Hopkins University: The Role of Vasomotor Spasm in Peripheral Arteriosclerotic Disease Following Sympathectomy.**—In forty patients with arteriosclerotic peripheral vascular disease, lumbar sympathectomy has been performed, with results suggesting that the spastic element plays a role in the production of intermittent claudication, pain, and gangrene.

## Book Review

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Always keenly alert and responsive to the students' needs, it is not surprising that he should be one of their best loved teachers.

Chiefly concerned in the progress of surgery and anxious that its teaching and practice at home should not suffer by comparison with those of other countries, Dr. Castro Villagrana, following the example of his lamented preceptor, Dr. Ulises Valdez (an honorary fellow of the American College of Surgeons), sought opportunities early in his career for observation and technical improvement in the great surgical clinics of the United States. How he gathered a rich harvest by his visits to the surgical centers of St. Louis, Chicago, Rochester, Minn., Baltimore, New York City, and Boston, is graphically told in paragraphs glowing in admiration for the work of the Mayos, Crile, Cushing, Dandy, and many others of whom he speaks collectively as the "Titans" of American surgery. He returned to Mexico deeply impressed with the splendor and vast resources of American medical schools and hospitals, the solidarity and marvelous rise of surgery as a specialty, the vast multiplication of surgical societies, and the creation of examining boards to test the qualifications of its candidates for practice; the standardization of hospitals inaugurated by the American College of Surgeons, the American Medical Association, and with it the enormous progress in surgical and hospital care which these great institutions had accomplished.

The opportunities for the special training and education of surgeons impressed him as being greater and more liberal in the hospitals of the United States than anywhere else in the world. His admiration for the American nurse evokes an outburst of praise, virtually an apotheosis, which could be well quoted in its entirety as an eloquent salutory for a graduating class in American training schools.

The author's observations in this and other journeys to the United States are characterized by a remarkable clearness of observation, total absence of prejudice, a discerning judgment, and a friendly appreciation of what is best in our institutions. That these observations have had their influence in his own country is quite evident in the over-expending program of hospital construction and rehabilitation and professional organization that is so notable in Juarez and other great hospitals of the Mexican metropolis.

Years later, in another journey to the United States, he stopped with several members of his staff to study the new Charity Hospital, in New Orleans, La., which was then under construction, and the medical institutions of the city, which, more than any other in North America, holds the greatest appeal to the Latin American traveller.

It was then that, through a happy circumstance, well described in this book, Dr. Castro Villagrana and his party arranged to meet Dr. Matas whose authority in vascular surgery had been long recognized in Mexico, where his operations for the cure of aneurysm were taught in the medical schools.

Indubitably one of the most fascinating chapters of the book is the author's brilliant portrayal of Dr. Matas. With glyptographic keenness the author first presents his impression of the general appearance and the noble beneficent countenance of Dr. Matas. As he unfolds his character study of this master surgeon, there is brought to light in gleaming and transpicuous rhetoric his multifaceted charming personality. In worshipful admiration he vividly portrays Dr. Matas' keen sense of humor, his effervescing vivacity, his beneficent cordiality, his contagious enthusiasm, his innate modesty, his linguistic perfection and facile eloquence, and his amazing knowledge of music, art, and history. In brief biographical sketch he traces concisely Dr. Matas' successful career from a young surgeon to that noble pedestal reserved for those whose life has been devoted to an eager and unceasing effort to benefit mankind. Referring succinctly to the numerous innovations and advances that have characterized his surgical enterprise, his perspicacious clinical and experimental investigations, and his invaluable contributions on surgery of the vascular system which

have made his name inseparably linked with this branch of surgical endeavor, in deservedly glowing terms, the author's tribute clearly reflects the world-wide appreciation of Dr. Matas.

The international amenities and friendships that resulted from this visit to New Orleans and Dr. Matas' cordial reception are stressed by the author in his reflections on the often unsuspected benefits that accrue to the nations from the interchange of medical relations, the medical man in his modest sphere officiating as a true ambassador of peace in a troubled world sown with the seeds of hatred, discord, and destruction.

In 1938, an opportunity to visit the great surgical clinics of Europe came with the triennial congress of the International Society of Surgery (*Société Internationale de Chirurgie*) held in Brussels, September, 1938, to which he had been officially and automatically delegated as chairman of the Mexican branch of this world-wide and truly representative international organization. Furthermore, the fact that his friend, Dr. Matas, as president of the Society, would preside over the congress, gave an additional incentive to attend it.

The narrative of Dr. Castro Villagrana's odyssey through the surgical clinics of Europe begins in London and continues for five chapters devoted to the surgeries of the continent, with long stops in Paris, Rome, Bologna, Padua, Vienna, Munich, Berlin, Dresden, Hamburg, and ending in the Congress at Brussels, which alone furnished him a complete cross section as it were of the best in the world of surgery.

Throughout this varied and colorful travelogue, the narrative moves along with all the animation of a technicolored cinema in which the master surgeons of the world are depicted in their typical surroundings and most characteristic bodily and mental attributes. Dr. Castro-Villagrana reveals his artistic, literary, and journalistic ability by the ease with which he transmutes into words whatever he visualizes. His first thought immediately after his introduction to the surgeon and his clinic, whether in his operating theater or in his private study, is to secure a mental snapshot that is to serve later for his comments and reflections on the man and the scene, always informative, biographic, and often meditative and philosophic. In this way his travelogue becomes a portrait gallery of master surgeons and of their characteristic environment, all told with a simplicity, fairness, and kindness, which make his impressions and judgments worthy of trust and confidence.

The International Congress at Brussels, with its splendid aggregation of the elite of European and International Surgery, afforded an excellent opportunity to Dr. Castro Villagrana to exercise his literary talents as a word painter to great advantage. In fact, his miniature sketches of the thirty and more members of the International committee assembled from every quarter of the globe, seated around the council table, suggest a large mural of mosaic tablets in which the faces of each one of the delegates can be plainly recognized in the word pictures of his vigorous strokes.

In this book the scientific proceedings of the Congress, which covered great discussions on some of the most vital issues in contemporary surgery (arterial hypertension, pulmonary surgery, bone grafting, etc.) are interestingly described in a language which is technically correct and yet thoroughly intelligible to nonprofessional readers. The program for the Twelfth Congress, which was to have been held in Stockholm this September (1941) under the local management of Dr. Hylmette and his Swedish colleagues, had been planned for a scientific feast of unsurpassed interest for the surgeons of the world, but the unexpected death of the lamented Prof. Hylmette, no doubt precipitated by the menace of a Nazi invasion of Sweden, has shattered all prospect of a congress in Europe for probably some years to come. Fortunately, the great organization, founded in 1905, is built on a foundation as immutable as the Rock of Ages, and is too well rooted in all civilized

countries, including the United States and Canada, to suffer more than a temporary suspension of its international functions.

We may rest assured that the *Société Internationale de Chirurgie* will pursue its magnificent traditions and manifest destiny when the tempest now sweeping over the suffering and delirious world has blown over.

Finally, to close this very inadequate notice of Dr. Castro Villagrana's fine book, we must touch, if only for a moment, upon his last chapter, "On the Surgeon and his Responsibilities," which sums up the most profitable lessons of his peripatetic experience.

In the vast surgical panorama unfolded by his travels, he has been struck by the constantly increasing importance of surgery in the social order, by the solidarity of its organizations and by the variety of its practitioners; none seemingly perfect but many great, and the greatest always those who never ceased to strive and labor honestly and sincerely for their own self-improvement in the service of their fellows and their art.

Whatever his exteriorizations, the surgeon must possess at least three fundamental qualities for success: *security or safety*, born of knowledge, skill, experience, and moral conscience; *gentleness*, kindness and tenderness with firmness, which comes from respect of human life and for the flesh itself, which the surgeon molds, trims, and fashions to accomplish his curative and reparative ends; and *simplicity*, which means directness, straight paths, not complicated or circuitous detours in thought or action, not burdened with time-wasting superfluities.

And those are the qualities which, according to those who know him best, are most distinctive of the author himself.

In conclusion, Dr. Castro Villagrana has produced a book that honors the surgical literature of his country, and that is elevating to the dignity and moral tone of surgery in general. In its ideology and literary quality it is essentially the product of a Latin mind; in its spiritual uplift, it is the expression of the noblest aspirations of mankind as voiced by one of the most fervent devotees of the cult of Esculapius.

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## Original Communications

### THE TREATMENT OF WAR BURNS

SURGEON REAR-ADMIRAL CECIL P. G. WAKELEY,\* C.B., D.Sc., F.R.C.S.,  
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BURNS and scalds form probably the earliest wounds treated by mankind. They have been known in ancient methods of warfare, and have formed quite a high casualty list in modern campaigns. Yet, never until the present conflict have burns and scalds been so numerous. There are many reasons for this great increase. First, the present war as the Germans are waging it, is a total war, and the bombing attacks are indiscriminate, and therefore the civil population, often women and children, may suffer the most. Second, the greatly extended use of mechanical transport with its oil fuel has been responsible for an increase in burns and scalds among the general public. Third, in the Navy, Army and Air Force, with their greatly extended use of petrol, and the fact that dive bombing on the warship and tank is a common procedure, the casualties due to burns have multiplied.

In the war of 1914-18 a large proportion of burns in the fighting services were caused by cordite, largely due to backflash down the ammunition shafts of fighting ships. This cause has been eliminated for all practical purposes in this war, owing to the fact that with the present mechanical arrangements, backflash is now impossible, and so cordite burns are rare. The common causes of burns and scalds as seen in the present war are petrol, burning oil, phosphorus pipes, electric burns due to severed cables or short circuits. Quite a number of bad burns have occurred among the fire fighting personnel, due to the intensive heat of burning buildings ignited by incendiary bombs. In a large collection of cases burns and scalds are the only injury present, yet on the other

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hand, there are always a number of cases both among the civilian population and in the fighting services, where the burns are complicated by open wounds or fractures. However in quite a proportion of burns in the Royal Navy the commonest complication is "blast lung" a condition which varies from a triviality to a most serious and fatal manifestation. Another complication which is not too well-known is fat embolism; this is found to be present in 40 per cent of burn cases which have proved fatal.

In times of peace the treatment of burns is quite standardized and straightforward, and most of the cases receive hospital treatment within one hour of the accident; therefore the results should be better and the mortality lower than those treated under war conditions. Again burns and scalds in peacetime are frequently the only lesion to be treated while in modern warfare there are often associated injuries. In this war there is the added complication of blast injuries both in civilian and service burns, because so many are caused by bomb flash.

During the last fifteen years much research has taken place concerning burns. This was initiated by Davidson, of Detroit, in 1925, who introduced tannic acid in the treatment of burns. The coagulation of the burnt area by tannic acid reduced the mortality of burns enormously, and prior to the war was universally used for all cases with great success. However, under war conditions burns do not always get immediate attention and sepsis is a very common complication.

#### CLASSIFICATION OF BURNS

Dupuytren described six different degrees of burns as follows:

The *first* degree consists merely in a scorch or superficial congestion of the skin, without destruction of tissue; the part may for a time remain red, painful and prone to ulceration.

In the *second* degree the cuticle is raised from the cutis, and a bleb or blister results. When this bursts, and the cuticle is removed, the cutis vera, red and painful, is exposed below.

In the *third* degree the cuticle is destroyed, as is also part of the cutis vera, but the tips of the interpapillary processes, including the exquisitely sensitive nerve terminals, are laid bare and left intact; consequently this is the most painful form of burn. The deeper structures of the skin, viz., the sweat and sebaceous glands, and the hair follicles, are not destroyed, so that although the surface during the healing process becomes covered with granulations, since there are so many surviving epithelial elements from which it can grow, the integument is very rapidly replaced. The cuticle is able to form, not only from the edge, as must occur whenever the whole of the cutaneous envelope is destroyed, but from innumerable foci scattered over the wound surface. The resulting sear, though often white and visible, undergoes no contraction; it is supple and elastic from containing all the elements of the true skin.

In the *fourth* degree the whole thickness of the integument is destroyed as well as part of the subcutaneous tissues. In the *fifth* the muscles are also involved, whilst in the *sixth* the whole limb or other affected part is completely charred and disorganized.

While this classification has been in use during the last one hundred years, yet it is a little too cumbersome and from a practical standpoint it is better to consider only three degrees: the first being an erythema, the second causing destruction of the epidermis with or without vesication, the third degree causing destruction of the whole skin and possibly some or all of the deeper tissues.

The treatment of burns is in reality a threefold problem. First, the saving of life; second, the local treatment of the burned areas; and third, the preservation of function of the parts involved.

In every case of burns there is always some shock present and this must be dealt with before any form of local treatment is attempted.

#### TREATMENT OF SHOCK

This consists in the early administration of morphia in adequate doses. Men require  $\frac{1}{3}$  gr. and this should be repeated if pain is not relieved. Warmth and rest are just as essential as the relief of pain and can be easily given under most conditions. Shock cradles and electric blankets are most useful in warming up shocked patients. Fluids by mouth should be encouraged but in extensive burns this is not sufficient in itself to make up for the plasma lost from the surface of the burnt area and for that which accumulates in the tissues. By animal experiment it has been shown that this plasma loss is greatest in third-degree burns, and amounts to over 70 per cent of the total blood volume in cases in which one-sixth of the body surface has been burnt.

The amount of plasma lost from the surface of the burnt area is quite small in comparison with the amount that accumulates in the tissues. This fluid imbalance is a shift of fluid rather than an external loss. The result of this fluid shift is a definite fall in blood pressure. Tissue fluids deficient in protein pass into the blood vessels in an attempt to maintain the volume of plasma in circulation; this, however, results in a lowering of the concentration of protein in the plasma. There is also a high urinary output of nitrogen due to the destruction of protein. The plasma loss causes a very definite hemoconcentration and it has been quite common to find that the hemoglobin percentage is 120 to 140 in extensive burns in the Royal Navy. The introduction of citrated plasma and reconstituted serum has reduced the mortality of war burns very considerably. Dried serum can be carried on any warship and it can easily and readily be converted into fluid by the addition of the requisite amount of distilled water. The reconstituted serum may be of normal concentration, twice normal concentration or four times normal concentration (Fig. 1).

hand, there are always a number of cases both among the civilian population and in the fighting services, where the burns are complicated by open wounds or fractures. However in quite a proportion of burns in the Royal Navy the commonest complication is "blast lung" a condition which varies from a triviality to a most serious and fatal manifestation. Another complication which is not too well-known is fat embolism; this is found to be present in 40 per cent of burn cases which have proved fatal.

In times of peace the treatment of burns is quite standardized and straightforward, and most of the cases receive hospital treatment within one hour of the accident; therefore the results should be better and the mortality lower than those treated under war conditions. Again burns and scalds in peacetime are frequently the only lesion to be treated while in modern warfare there are often associated injuries. In this war there is the added complication of blast injuries both in civilian and service burns, because so many are caused by bomb flash.

During the last fifteen years much research has taken place concerning burns. This was initiated by Davidson, of Detroit, in 1925, who introduced tannic acid in the treatment of burns. The coagulation of the burnt area by tannic acid reduced the mortality of burns enormously, and prior to the war was universally used for all cases with great success. However, under war conditions burns do not always get immediate attention and sepsis is a very common complication.

#### CLASSIFICATION OF BURNS

Dupuytren described six different degrees of burns as follows:

The *first* degree consists merely in a scorch or superficial congestion of the skin, without destruction of tissue; the part may for a time remain red, painful and prone to ulceration.

In the *second* degree the cuticle is raised from the cutis, and a bleb or blister results. When this bursts, and the cuticle is removed, the cutis vera, red and painful, is exposed below.

In the *third* degree the cuticle is destroyed, as is also part of the cutis vera, but the tips of the interpapillary processes, including the exquisitely sensitive nerve terminals, are laid bare and left intact; consequently this is the most painful form of burn. The deeper structures of the skin, viz., the sweat and sebaceous glands, and the hair follicles, are not destroyed, so that although the surface during the healing process becomes covered with granulations, since there are so many surviving epithelial elements from which it can grow, the integument is very rapidly replaced. The cuticle is able to form, not only from the edge, as must occur whenever the whole of the cutaneous envelope is destroyed, but from innumerable foci scattered over the wound surface. The resulting scar, though often white and visible, undergoes no contraction; it is supple and elastic from containing all the elements of the true skin.

TABLE I

HEMOGLOBIN % HALDANE	BLOOD VOLUME (LITERS)	PLASMA VOLUME (LITERS)	ESTIMATED DEFICIT IN PLASMA VOLUME (C.C.)
100	5.0	3.0	-
105	4.75	2.75	250
110	4.55	2.55	450
115	4.35	2.35	650
120	4.15	2.15	850
125	4.0	2.0	1,000
130	3.85	1.85	1,150
135	3.7	1.7	1,300
140	3.55	1.55	1,450
145	3.45	1.45	1,550
150	3.35	1.35	1,650

For those cases in which shock is severe intravenous adrenal cortical hormone (cortin) 2 c.c. should be given repeatedly, and oxygen administered by a Boothby mask enables the patient to obtain this in the alveolar air. In cases which are complicated by "blast lung" this form of administering oxygen is most advantageous. In the Navy, where Boothby masks have been in use for all badly shocked burn cases, their value has been inestimable.

*First-Aid Treatment.*—Not until antishock measures have been instituted should any local treatment be attempted. Preliminary cleansing is often impossible as a first-aid measure on board ship during action, or the inside of a tank or aircraft, therefore the use of one of the medicated jellies which are soothing in their application is indispensable. Gentian violet and merthiolate, amertan jelly, tannafax or tannax, all have their advocates, but my preference is the gentian violet preparation. The jelly should be liberally applied on two or three layers of gauze which are then placed over the burnt area and retained by a few turns of a bandage. This first-aid dressing can be left in situ until the patient reaches hospital, unless any areas are seen which have become moist and then they should be retanned with the jelly. Burns of the face, although the gentian violet preparation answers quite well, are probably better treated with cod-liver oil, which is not only an antiseptic but has a high vitamin content. If the eyes are burnt, drops of castor oil containing 1 per cent cocaine should be instilled.

In those cases in which associated injuries are present, such as a wound or a fracture, the gentian violet jelly should be applied to the wound as well as to the burn. If the extremities are involved and compound fractures are present, the limb should be put up in plaster of Paris after the wound and burnt areas have been liberally dressed with the gentian violet jelly.

*Hospital Treatment.*—Some cases of burns will arrive in hospital after first-aid treatment has been carried out while others will be admitted

Any patient suffering from burns must have his hemoglobin estimated and if the percentage is above 100 then plasma should be given. Witts recommends the giving of plasma to any patient in whom the hemoglobin is 10 per cent above the probable previous value; if this was 100, the plasma loss can be calculated from the formula:

$$\frac{H6}{100} = \frac{5}{5-x} \text{ where } x \text{ is the plasma lost in liters.}$$

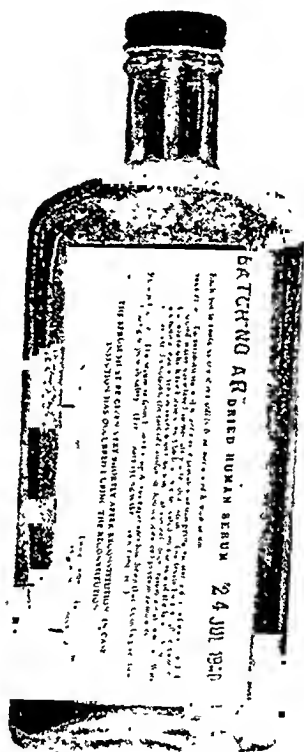


Fig. 1.—Dried human serum. Each bottle contains the dried solids from 200 c.c. of human serum. *Solution:* To reconstitute add under sterile precautions nonpyogenic sterile distilled water; i.e., B.P. distilled water autoclaved immediately after distillation. The levels for the different concentrations to which the bottle should be filled are indicated on the side of the label. *Solution* at four times normal concentration takes about sixty minutes, at normal concentration about ten minutes. With concentrated solutions, the rate of transfusion should not exceed 50 c.c. in ten minutes. *Blood Group:* The serum is from Blood Group A, but experience has shown that it can be given to all blood groups with safety. (Preliminary typing is therefore not required.) The serum must be given very shortly after reconstitution, in case infection has occurred during the reconstitution. The higher level on the side of the label indicates normal concentration. The middle level on the side of the label indicates twice normal concentration. The lower level on the side of the label indicates four times normal concentration.

Plasma of the calculated amount is given quickly and more is given later by slow continuous drips to make good the loss by exudation.

Using the above formula Black has worked out the estimation of plasma volume reduction; this has proved of real value to those who have had to treat a large number of serious burn cases.

If the burn has been extensive, and of the third degree, healing will not have taken place, but a large granulating area will be exposed after the tan is removed. This area should be treated with a saline dressing for a day and then skin grafted. *There are still too many cases of burns which are allowed to heal by granulation with its subsequent keloidal and fibrous tissue formation.* On the backs of the hands and fingers in

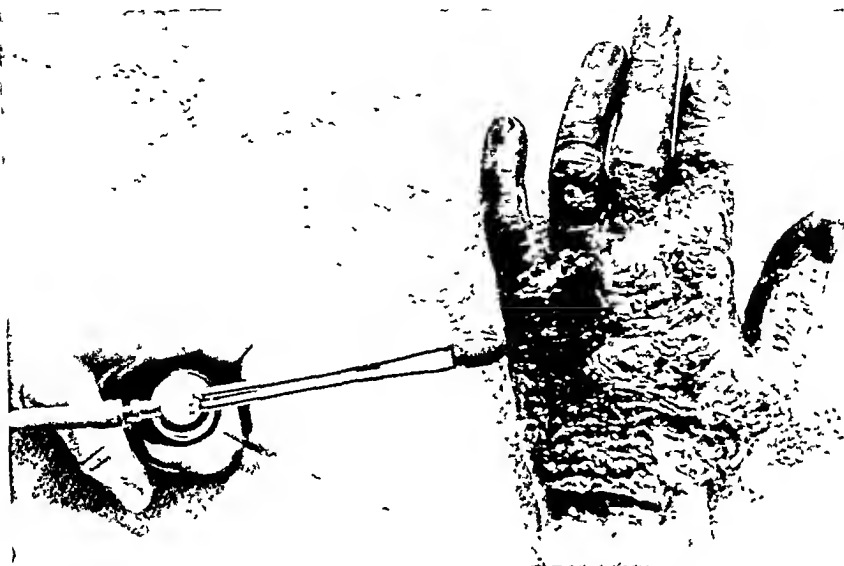


FIG 2—Application of triple-dye by means of a spray

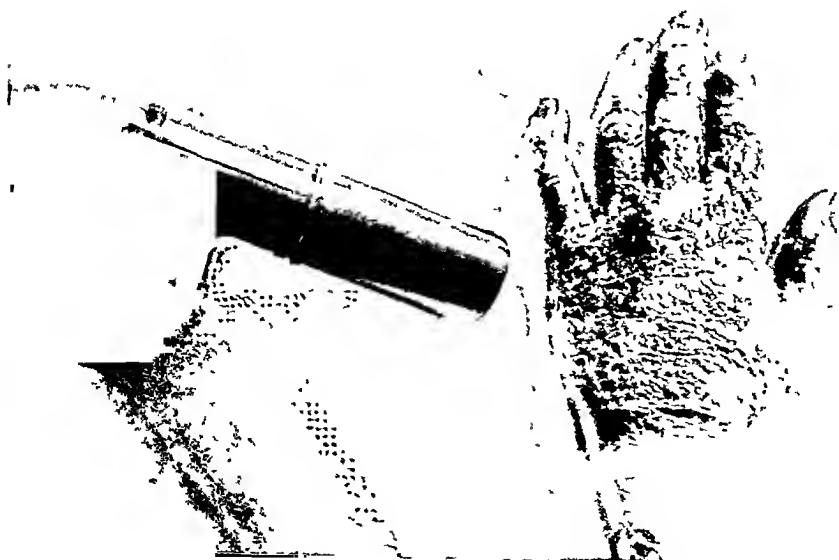


FIG 3—Method of drying the triple-dye solution by means of an electric hair dryer.

without any treatment having been given. Some Naval cases have arrived on board hospital ships having spent some time in the sea after having been burnt and have suffered little from shock or pain and after local treatment to the burnt areas have made excellent recoveries. The experience gained from a number of such cases has convinced many medical officers of the great value of saline dressings, especially in the treatment of burns of the face and hands, but it is essential that the saline dressings are kept moist.

The local treatment of war burns demands the strictest aseptic precautions or sepsis will occur. The surgeon should wear a sterile gown, mask and gloves while dressing and inspecting burns. If possible, burn cases should be treated in a separate ward and, if circumstances permit, in separate cubicles divided from each other by glass or mica partitions. This is the ideal method of treating war burns, as the likelihood of mixed or cross infection is reduced to the absolute minimum. From an experience of well over 1,000 cases of war burns I am convinced that infection is the commonest cause of the toxemia in burns, and that the commonest organism is the hemolytic streptococcus. This organism has been repeatedly grown from blister fluid in the burnt areas in cases which arrive in hospital some hours after the injury. These observations fully confirm the work of Aldrich in 1933, and it is for these reasons that the triple-dye method of treatment is given priority in the many methods of treatment of war burns.

#### TRIPLE-DYE METHOD

The patient should be anesthetised with gas and oxygen and all loose and blistered skin should be cut away and the wound area swabbed with warm saline solution. The burnt area is then dried with an electric hair drier and an aqueous solution of triple-dye (2 per cent gentian violet, 1 per cent brilliant green, 0.1 per cent neutral acriflavine) is sprayed on the surface (Fig. 2).

This is then dried and a second application applied, which in turn is dried (Fig. 3). Usually two applications are sufficient to produce a nice thin supple tan, which is quite adherent everywhere and no sepsis appears around the edges of the tan. In those cases in which sepsis is evident owing to inefficient cleansing and insufficient tanning, an anesthetic should be given and the area retained. It is not always necessary to remove the pre-existing tan.

The dyed burnt areas are not covered with any dressings but the patient, with the exception of the head, is shrouded with a hot-air cradle. Each day the tan is inspected and any moist areas receive another application of the triple-dye. Usually by the end of ten days the tan becomes quite loose and falls off, leaving a healed wound (Figs. 4 and 5).

third-degree burns early skin grafting makes all the difference between success and failure. The question of the value of sulfanilamide in the treatment of burns is somewhat of a vexed one. I consider that it should be given by mouth for three days only and never used as a powder and dusted over the burnt area. While the sulfanilamide is being administered the patient often vomits and cannot take the increased protein diet which is so essential to his recovery. It must also be remembered that fully two-thirds of the body sulfur must be replaced. The best method of sulfur replacement is by a liberal diet of eggs and these cannot be taken during the sulfanilamide treatment.

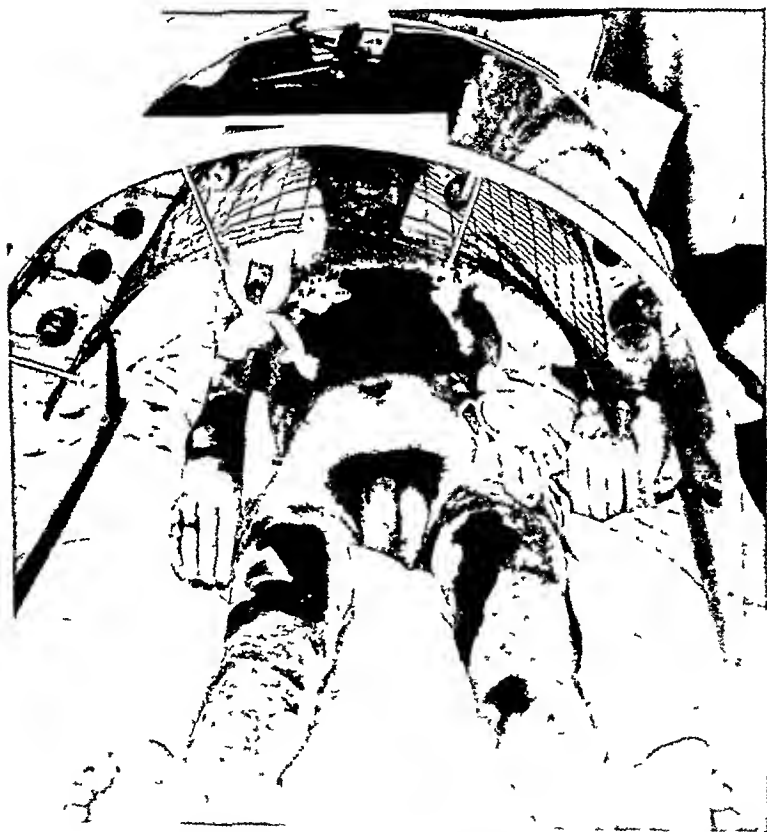


Fig 6—Extensive burns of trunk and extremities treated with tannic acid. The tan can be seen on legs and abdomen. No dressings were used, the patient was nursed under a heated cradle.

#### TANNIC ACID TREATMENT

This treatment should not be given until shock has been combated. The actual cleansing of the burnt area is identical with that used before the triple-dye is applied. After cleansing with saline solution the area is dried and 1 or 2 per cent gentian violet is applied by swabs and dried by a current of hot air from an electric dryer. A solution of 5 per cent





Fig 4—Burn of face due to bomb-flash, a typical "blast" injury. This patient suffered from "blast lung" as well. Photograph taken five hours after injury.



Fig 5—Bomb-flash burn of face ten days after injury. Treated with triple-dye. Same case as shown in Fig 4.



Fig 8—Third-degree burn of hand treated with tannic acid      Terminal necrosis of the fingers can be seen



Fig 9—Skiagram of hand depicted in Fig 8, showing necrosis of the terminal phalanges

tannic acid is then applied followed by a 10 per cent solution of silver nitrate (Fig. 6). A firm hard tan is quickly produced by this method and it is suitable for burns of the trunk but should never be used on the hands or face owing to the bad results that ensue (Fig. 7). Numerous cases which have occurred in the present war have produced ample evidence that under the unyielding tannic acid coagulum applied to the hand and fingers an edema develops to a degree which seriously embarrasses the circulation in the fingers with the production of crippling deformities (Figs. 8 and 9). This is the result of the treatment and not of the burn.

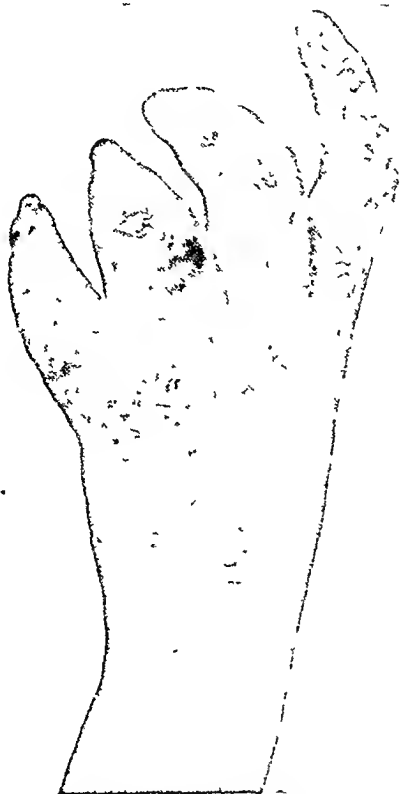


Fig. 7.—Third-degree burn of the hand treated with tannic acid. Note the attenuated fingers and fixed flexion. A result due to the unyielding tan.

After the application of the tannic acid the whole affected area should be kept at rest and the limbs should be suspended or splinted. The patient is nursed in a tented bed containing heating elements and great care should be taken to maintain a dry, unbroken surface.

As a rule minor degrees of sepsis can be controlled by gentian violet sprayed on the affected areas after removal of the overlying crust, but if the entire surface becomes infected the tan must be removed by soaking with saline solution or in a saline bath. Retanning should never be under-



Fig 10—Mixed burn of the hand of an airman. Photograph taken just prior to treatment with triple-dye

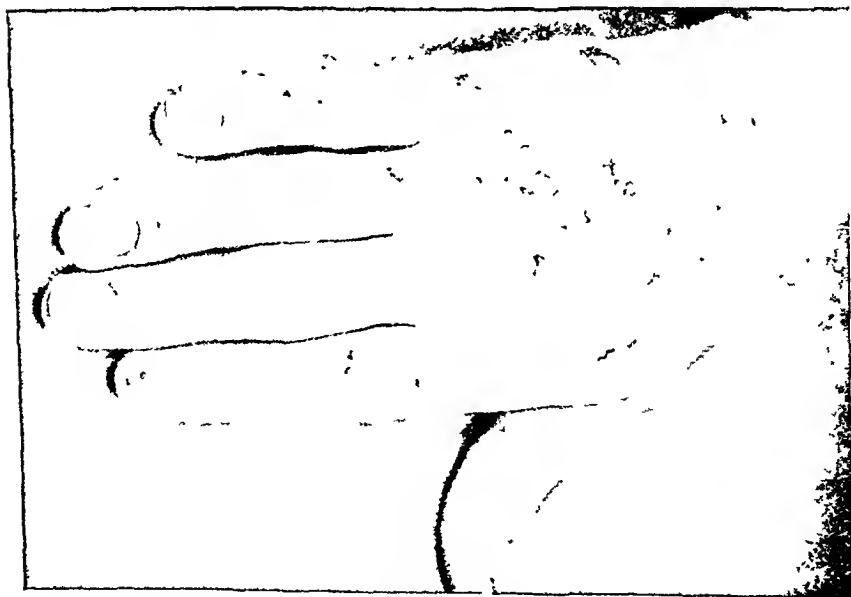


Fig 11—Mixed burn of hand treated with triple-dye. Three weeks after injury. Same case as shown in Fig 10.

taken. In third-degree burns of large area skin grafting must be performed if scarring is to be prevented.

In the Royal Navy and in the Royal Air Force a large proportion of burns are limited to the hands and face as the clothing protects the rest of the body. It is very essential that full functional results should be obtained without scarring otherwise a considerable proportion of valuable personnel would be invalidated from these Services.

*Burns of the Hands.*—There can be no doubt whatever that the best preliminary dressing for burns of the hands is a saline bath. The hands should be immersed in a bath twice a day and the patient encouraged to move his fingers in the bath. A saline pack is applied after the bath and this is kept moist and allowed to fall off in the next saline bath. By such a process trauma is reduced to a minimum and there is no pain from changing the dressings. After three or four days of this treatment triple-dye is used and when this begins to loosen in ten or twelve days the burnt area will be found completely healed (Figs. 10 and 11).

Saline packs however cannot be given as a first-aid dressing and so the majority of cases of burns of the hands have to be treated with a gentian violet jelly; excellent results have been obtained from this treatment. Many a time we have seen members of the trawler crew who have been bombed at sea and burnt either by bomb flash or scalded by a burst steam pipe in the engine room, arrive in port four days after the attack. The prompt use of gentian violet jelly and its repeated application has allowed these members of the crew to carry on with their work until they reach port.

Burns of the third degree in which the whole thickness of the skin is destroyed, should be treated with saline baths if possible and then early skin grafting. Sepsis must be eliminated at all cost because of the contractures that are bound to follow. An excellent dressing for burnt hands is "tulle gras" or "jelonet" or "nonad tulle" all these are made of woven open-mesh gauze, saturated with petroleum jelly and balsam of Peru. These dressings are vitaminized and sterile and are packed in suitable tins. After soaking the hands in a saline bath for an hour the burnt area is covered with one of these sterile vitaminized dressings over which is placed some sterile gauze wrung out of normal saline solution. This saline gauze is replaced every two hours without in any way interfering with the underlying dressing. It is very important that the superficial saline dressing should not become dry, and that the dressing should not stick. The hands are placed on wire splints in a position of rest with slight dorsiflexion of the wrist and slight flexion of the fingers. Two or three saline baths are given each day and the dressings are allowed to float off in the bath thus causing no pain to the patient or trauma to the healing wound.

and 13.) In several third-degree cases seen earlier in the war corneal ulceration and perforation of the globe were seen owing to sepsis occurring under the tan. The elimination of sepsis is of prime importance and early skin grafting is essential when the whole thickness of the skin is destroyed.

#### THE ENVELOPE METHOD OF TREATING BURNS

This method which was devised by Surgeon Lieut. Commander Bunyan R.N.V.R., and has been employed in many hospitals has certain advantages, the greatest being the painlessness of its application.

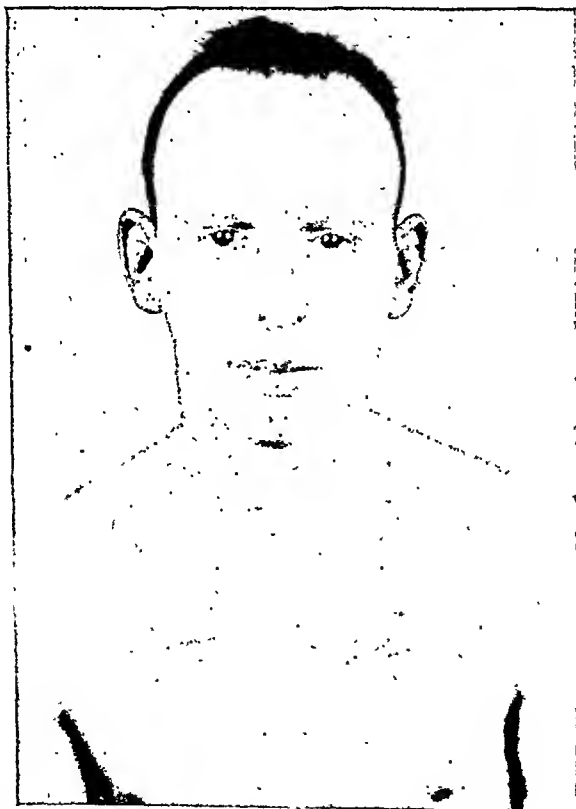


Fig. 13.—Mixed burn of face treated with triple-dye, fifteen days after the injury. Same case as shown in Fig. 12.

The treatment consists of a primary irrigation of the burnt area with a 10 per cent solution of electrolytic hypochlorite at 100° F. This irrigation is performed under anesthesia in an operating theater and it should be very thorough. The irrigation removes all surface contamination, much of the charred tissue, and all the exudates and at the same time kills the majority of the bacteria that may be present.

Specially coated silk envelopes are then put on the burnt area or limb. The envelopes are made of fine pure silk cloth coated with

If the burn has destroyed the whole thickness of the skin, then skin grafting should be undertaken without delay; otherwise contractures and scarring will result.

After healing has taken place it is very important that the newly formed skin should be adequately nourished and to this end some lanoline is rubbed into the area every night. This natural wool fat has a wonderful effect on the skin; it causes it to become thicker and more supple and increases its blood supply. It is a pity that the aftertreatment of burns has been so neglected in this respect. The inunction of lanoline should be continued for fully three months after the healing of the burnt area if good results are to be obtained.



Fig 12—Mixed burn of face treated with triple-dye.

*Burns of the Face.*—In burns of the face there can be no doubt that saline dressings are the best form of treatment if the patient can be transferred to hospital immediately after the injury. However this is rarely possible in the Services and therefore some first-aid treatment must be given. Gentian violet jelly has given excellent results in the Royal Navy as also has cod-liver oil which is antiseptic and has a high vitamin content. Tannic acid should not be used on the face as the burn cannot be watched sufficiently and early skin grafting may be delayed. (Figs. 12

mediately in hospital should be given a continuous constant temperature saline bath. The whole body is immersed in a bath filled with 0.9 per cent saline solution. The temperature of the water is controlled by a thermostat. The patient is left in the bath for an hour and then carefully removed to a heated, tented bed and the burnt areas are covered with a layer of tulle gras over which is placed some warm wet saline



Fig 15 —Extensive burn of leg treated by irrigation inside a Bunvan envelope.

gauze rolls The gauze should be frequently moistened with saline solution so that the dressing never becomes dry. Quite a number of the civil and service hospitals have installed these continuous saline baths because they have proved of real importance in the treatment of extensive burns, especially those in which the whole thickness of the skin is involved. When the burnt area becomes covered with granulation tissue, then the baths can be discontinued and skin grafting carried out.



synthetic resins which are unaffected by hypochlorites or boiling, and render the silk watertight.

After the envelope has been applied irrigation with hypochlorites is given twice or three times a day (Figs. 14 and 15). Between irrigations the wound is left undisturbed. This method has some definite advantages in the treatment of war burns. They are:

1. It can be easily and quickly applied.
2. The treatment is painless, there are no dressings, and the patients do not lose confidence or become depressed.

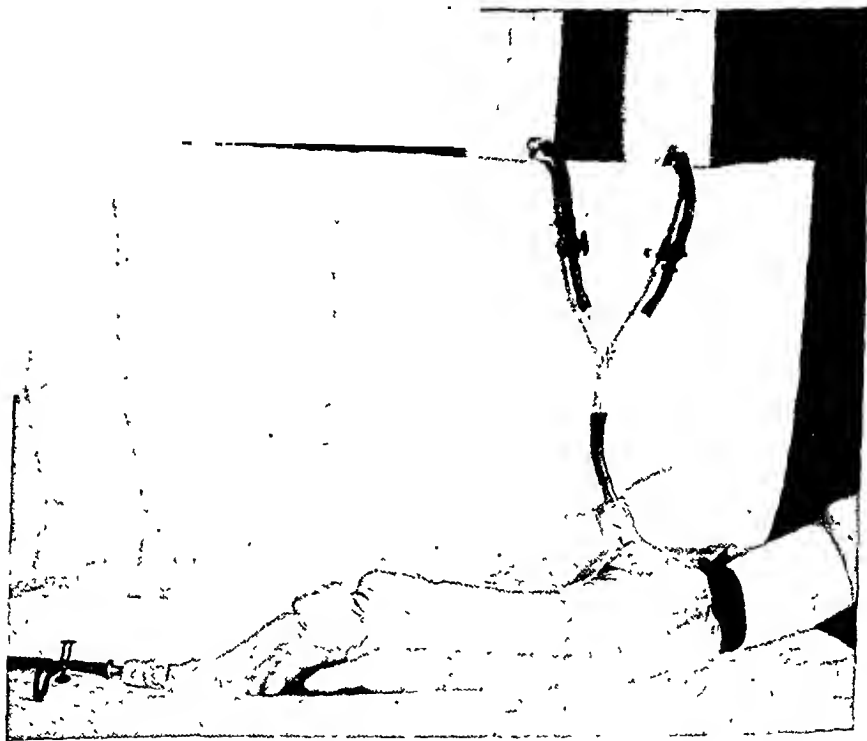


Fig. 14.—Burn of forearm and hand treated by means of Bunyan's envelope. Hypochlorites are run in from the jars above.

3. Rapid epithelialization takes place and can be seen through the envelope. Skin grafting can be performed at any time after irrigation with saline solution instead of hypochlorites.

4. The envelope allows of free movement of the limb without the fear of pain.

5. In the difficult cases where fractures exist as well as burns, this method appears to offer a solution. Treatment of ordinary compound fractures has proved successful.

*Extensive War Burns.*—A proportion of war burns involves a large area of the trunk and extremities. Such burns if they can be treated im-



Fig 17—Phosphorus burn of face Appearance on admission to hospital



Fig 18—Phosphorus burn of face a week after injury. Same case as shown in Fig 17

*Electrical Burns.*—These are not uncommon in wartime and they are due to broken cables, short circuits and the like, resulting from gun-fire or bombing attacks. While a certain number of this variety of burn prove fatal yet a large number recover if the initial shock is treated adequately. The appearance and size of electric burns will vary with the shape of the object carrying the electricity, but usually they are circular or elliptical areas (Fig. 16). The color of the burnt areas is grayish white, with a slightly raised periphery, a depressed center, and no surrounding area of hyperemia. They look glossy, feel smooth like



Fig. 16 —Large electrical burn of the anterior surface of the elbow. This was excised and skin grafted.

parchment and when on the fingers, result in the complete obliteration of the papillary lines over the area they occupy. By far the best treatment for these electrical burns is excision and full thickness skin grafting. Small electric burns require nothing more than the application of some gentian violet jelly.

#### BURNS DUE TO CHEMICAL WARFARE

1. *Mustard-gas burns* are very insidious and take a long time to heal so causing a long incapacity on the part of the patient. During the last war mustard gas was the most effective chemical agent used and it

area is then dried and treated with gentian violet jelly or triple-dye. Healing is slow and sometimes as long as six or eight weeks elapse before sound healing has occurred

2. *Liquid lewisite burns* may occur as separate entities or they may result from a mixture of mustard gas and lewisite. Lewisite is a heavy oil which is both a lung irritant and a vesicant. Penetration of the skin by lewisite is much more rapid than that of mustard gas. Erythema of the skin after a lewisite burn appears within thirty minutes and vesication is developed within twelve hours. The lewisite blister is more sharply defined than that caused by mustard gas, and contains an opaque fluid in contradistinction to the clear lipid fluid found in the mustard



Fig 20



Fig 21

Fig 20—Crude nitric acid burn of face. Two days after injury

Fig 21—Crude nitric acid burn of face three weeks after injury. Same case as shown in Fig 20

gas blister. Treatment consists in complete decontamination as with mustard gas, and a hot bath. Hydrogen peroxide should be applied to the burn area followed by triple-dye.

3 *Phosphorus Burns*—A small number of such burns have been treated in the present war, they result from the backflash of incendiary bombs containing phosphorus. Some are extensive; whereas, others are small and due to the presence of a fragment of shell containing this substance (Figs 17, 18, 19). Such small burns are liable to become deeper as the phosphorus continues its thermal action on the tissues. As a first-aid treatment a solution of 2 per cent copper sulfate should be

was a great casualty producer. It may be that in this war this gas will be used in the form of a spray from low-flying aircraft. Mustard gas in the pure state is a clear oily fluid with a slight mustard-like odor. It has great powers of penetration and will soak through clothes and boots, and cause a burn. On the skin the liquid mustard gas is not immediately painful and during the interim period before pain is caused the liquid penetrates the tissues rapidly, yet it may be some hours before an actual burn is seen clinically and marked itching ensues. There is



Fig. 19.—Phosphorus burn of face, three weeks after injury, showing complete healing. Same case as shown in Figs 17 and 18.

no absorption of the liquid gas into the general circulation and primary shock is absent. During the first twenty-four hours a large blister forms at the periphery of the burn, and if not incised will burst of its own accord. In the absence of sepsis there is little constitutional disturbance, but if sepsis does occur it may be very severe. Treatment of course demands the complete decontamination of the patient, including the burn. The clothing must be removed and the whole body should be washed thoroughly with bleaching powder solution (60 gr. to a pint). The burn

applied; this combines with the phosphorus and produces an inert chemical substance, so preventing any further damage. After the copper sulfate solution has been cleaned off with gauze some triple-dye is sprayed on the burnt area.



FIG. 24.—Keloidal scarring of arm and forearm eight months after an extensive second-degree burn. The immediate result was excellent. X-ray therapy considerably improved the condition.

4. *Crude Acid and Alkali Burns*—A fair proportion of burns due to strong acids or alkalies have been caused because of the repeated bombing of factories in this war. In a series of cases seen by me the patients were treated by immersion in running water followed by the application of triple-dye (Figs. 20 and 21). In almost every case it is the hands and face that are burnt because the clothing itself is protective.



Fig. 22.—Burn of hand six months after injury, showing attenuated skin with engorged blood vessels. Skin grafting should have been performed in this case.

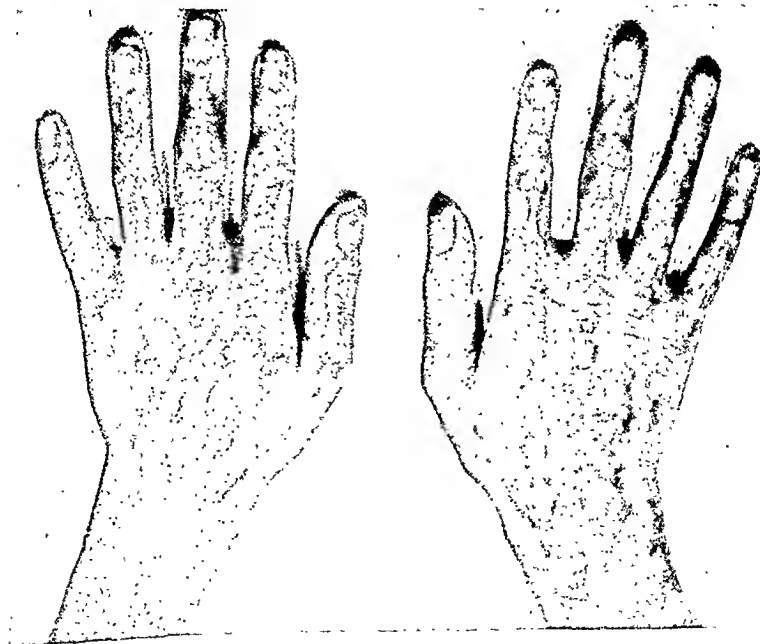


Fig. 23.—Keloidal scars of hands and fingers. Photograph taken six months after a mixed burn of the hand. Early skin grafting would have prevented this deformity.

with the result of his treatment when the patient is discharged from hospital and yet in six months' time the newly formed skin may have become keloidal and contractures may have taken place (Figs. 22, 23, 24).



Fig. 26 —Antiflash outfit for facial protection, the goggles and mask are held in place by elastic bands



Fig. 27.—Antiflash protection outfit, side view.

Further, the patient may be able to do his full work during the warm summer months, but in the cold of the winter the thin skin of the backs of the hands or the ears may crack and fissure and chilblains may form thereon, necessitating treatment and even invaliding from one of the fighting forces. This is a serious and significant point as men of the



5. *Phosgene Burns*.—These are quite superficial and cause an erythema or brown staining, but are quite insignificant in comparison to the rapidly fatal syncope produced by this gas.

The odor of phosgene is quite characteristic and resembles that of new-mown hay; and when recognized a gas mask should be put on at once and the recumbent position immediately adopted. The burn itself should

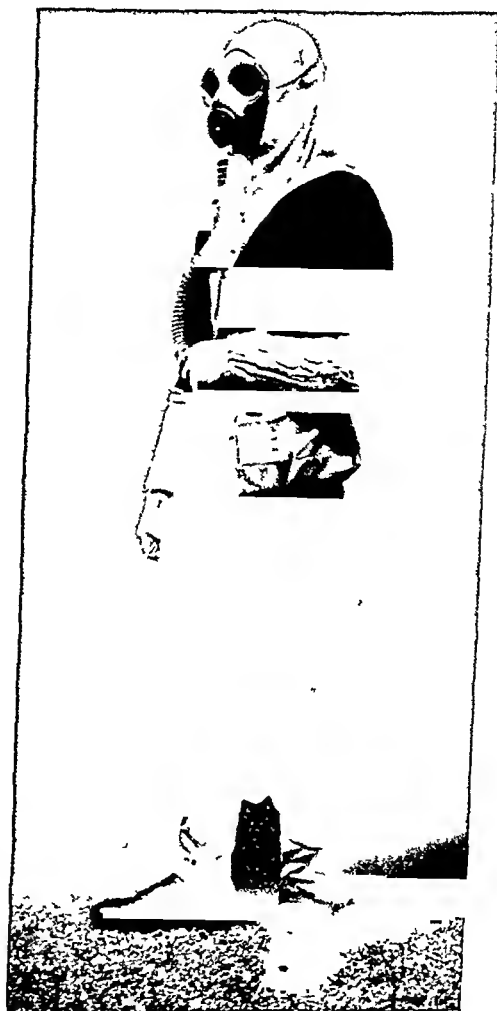


Fig 25—Antishock outfit including gas mask

be treated with sodium bicarbonate solution (5ii ad Q) and then dried after which gentian violet jelly can be applied.

*Final Assessment of War Burns*.—It is a great pity that a “follow up” of all burn cases has not been instituted in civil hospitals as is the case in the Royal Navy. It is most important to follow up patients suffering from war burns, because the medical officer may be very pleased

## SHOCK IN PERFORATED PEPTIC ULCER

A SURVEY BASED ON SOME 335 CASES FROM THE FOUR SURGICAL  
DIVISIONS OF BELLEVUE HOSPITAL FROM 1929 TO 1938

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IT IS often hinted and sometimes said that the patient with a perforated ulcer appears to be in shock.<sup>1-3</sup> This, however, conflicts with the theories presented in certain textbooks and those of some authors who have given attention to the problem.<sup>4-6</sup> In reviewing cases over a ten-year period in a large general hospital, an attempt has been made to present statistical evidence of the degree of shock found, the factors responsible for it, and its importance diagnostically, therapeutically, and prognostically.

### MATERIAL USED

An effort was made to include all cases, regardless of duration of perforation or subsequent treatment, provided that in each instance the diagnosis was established by operation or autopsy. Clinical observations and temperature and pulse and blood pressure recordings used here are those taken at the time of physical examination in order to precede medication or intravenous therapy. Although the temperature and pulse levels were noted in all but 2 of the cases, blood pressure recordings in 55 were either omitted or were taken subsequent to some form of treatment. Of these 55, however, only 3 presented one or more signs of shock. The size of the perforation was given in exact measurements in 279 cases, those recorded in inches being changed to equivalent metric figures for this paper. These figures are based on estimates made by the operators. Amount of fluid in the peritoneal cavity was noted by some observers as large, moderate, or small. Others gave an estimate in round numbers. Obviously these calculations are vague and inaccurate. They have been divided very arbitrarily into three groups, less than 800 c.c. being called a small amount of fluid, between 800 and 3,000 c.c. being termed moderate, and anything above this, large. In 61 patients the amount was not stated. In only a few was the presence of food particles noted or the time relationship between eating and rupture.

### INCIDENCE OF SHOCK

Shock, a word simple enough to define as a form of circulatory collapse marked by lowered blood pressure; weak, rapid pulse; subnormal temperature; pallor, sweating, and coldness of the skin existed with every sign present in very rare cases in this series. Altogether, 56

fighting services may have to go into cold climates, and in the Navy be exposed to bitter winds and rapid changes of temperature.

*Protection Against Burns.*—In the Royal Navy and in the Royal Air Force the vast majority of war burns involve the face and hands. In the Royal Navy this important fact has been appreciated since the battle of Jutland in 1916. At the present time an antiflash clothing for the head and hands is now served out to every fighting ship for the use of officers and men who are exposed to gun-flash or bomb-flash, and has resulted in a marked reduction in the number of burns. This outfit (Figs. 25, 26, 27) can be used in conjunction with a gas mask and is simple and easy in its application and does not impede the usefulness of the men at action stations.

It is a pleasure to record my indebtedness to Surgeon Vice-Admiral Sir Percival Nicholls, Medical Director General of the Navy, who has given me every facility to see and treat all varieties of burns during the present conflict.

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perforated while on the ward. Observations were recorded within two hours on 11 and within three hours on 15. Nine had blood pressure recordings taken subsequent to perforation and prior to treatment. Of these only 1 had a systolic pressure below 100 and he had been hemorrhaging severely. Six patients were described as being in shock, but 3 of them had pulse rates of 90 or less, and another had had a rise in systolic blood pressure from 104 on admission to 120 after perforation. It is unfortunate that the records for this group are so incomplete. Only 3 patients, however, showed any signs of shock, and the signs were

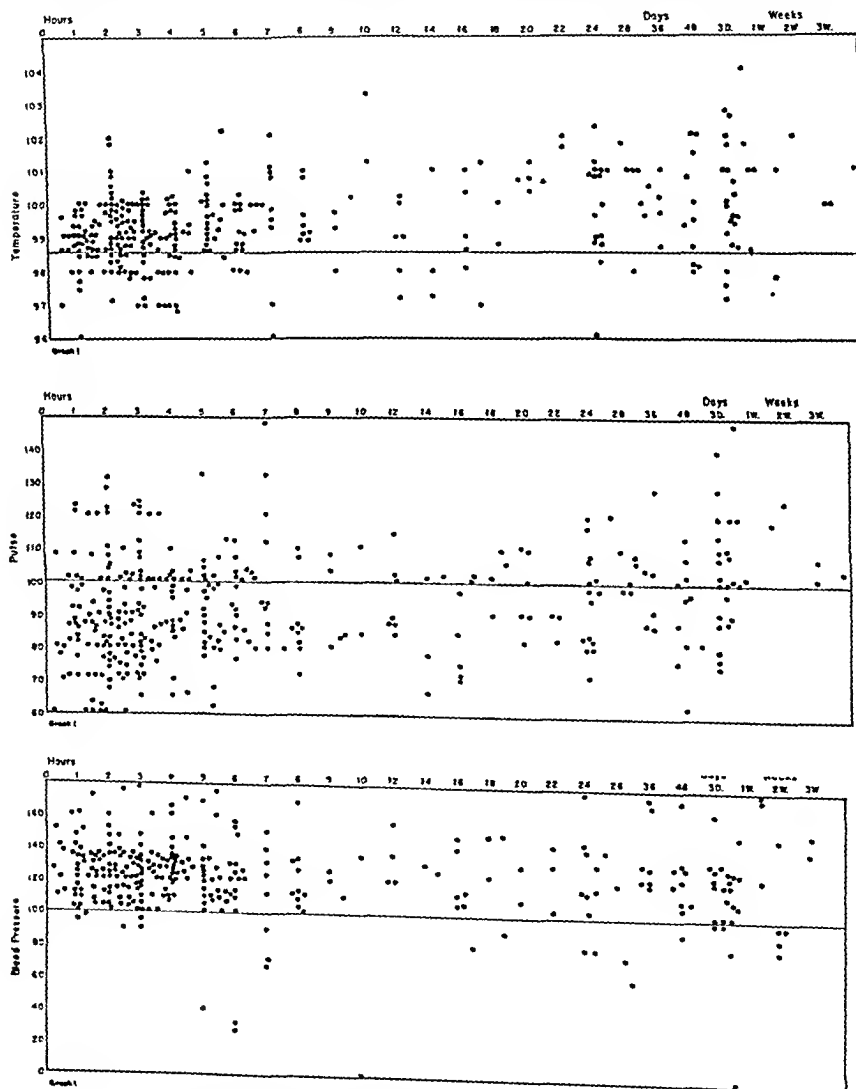


FIG. 1.—Temperature, pulse, and respiration of each patient at the time first observed after perforation are represented by dots in this graph.

patients, or 16.7 per cent, had subnormal temperatures; 129, or 38.5 per cent, had pulse rates above 100; 39, or 11.6 per cent, had systolic blood pressures of 100 or less; 22 were stated as being in shock regardless of accompanying signs; and 56 were noted to be sweating, cold, or pale, or to have a combination of these three. There were but 20 cases, or roughly 6 per cent, that combined a systolic tension of 100 or less, with either a rapid pulse rate (above 100) or a subnormal temperature or pallor, etc., or several of these. These 20 patients are the only ones who come near to the definition of shock, so they have been considered separately from the rest in an attempt to correlate their signs with perforation or other causative factors. There were but 3 of the 20 who presented the classical picture of shock as defined above without a sign missing. One of them suffered from hemorrhage; another was syphilitic with a very poor cardiac reserve; and the last one had had perforation three days before entry and showed frank peritonitis at operation. Four more individuals had no other etiologic factor than perforation upon which their signs could be blamed. They did not present a very convincing picture, however, for their blood pressures were above 90, their pulse rates between 78 and 108, and their temperatures ranged from 97.8 to 100.8°. Only 1 was listed by an observer as being in shock and one other was said to be cool and sweating. They did not approach the classical picture. Of the 13 remaining, 1 was quite drunk, 9 had full-blown signs of peritonitis, 2 were suspicious of peritonitis, and another was anemic from blood loss. All of these 13 and the 3 profoundly shocked patients died. It becomes apparent from these figures not only that true shock is rare in perforated peptic ulcer, but that in the presence of some signs of it there is probably an additional causative factor to be suspected. Peritonitis is the chief of these, being present in 12 patients out of this group of 20.

#### RELATIONSHIP OF SHOCK TO TIME

The duration of symptoms among these patients is extremely variable. In some the onset of rupture was but twenty minutes before examination; in others it was several weeks. The largest number was seen within the first six hours, but no less than 68 did not even arrive at the hospital until a day or more had elapsed. Although the signs of shock are infrequent, it is of some interest to attempt to find their relationship to duration of peritoneal insult, to the amount of fluid, and to the size of the ulcer. As Thompson<sup>8</sup> has pointed out, 69 per cent of perforations lie anteriorly; in other words, where the fluid is most free to escape into the general peritoneal cavity. Such being the case, will a patient with an early perforation be more apt to show signs of circulatory collapse following sudden insult, or will the signs be more likely to follow a prolonged flow and spreading infection? In this series some 16 patients

within the first two hours. High pulse rates are to be seen at both ends of the scale, with more elevated ones late in the disease, yet plenty of normal ones occur one or two days after onset. There are more sub-normal systolic pressures after twenty-four hours proportionately, but there are also numerous normal readings and plenty of low pressures in the first six hours. In Fig. 2 the pulse, temperature, and blood pressure recordings of the 20 cases in mild or severe shock are plotted to show

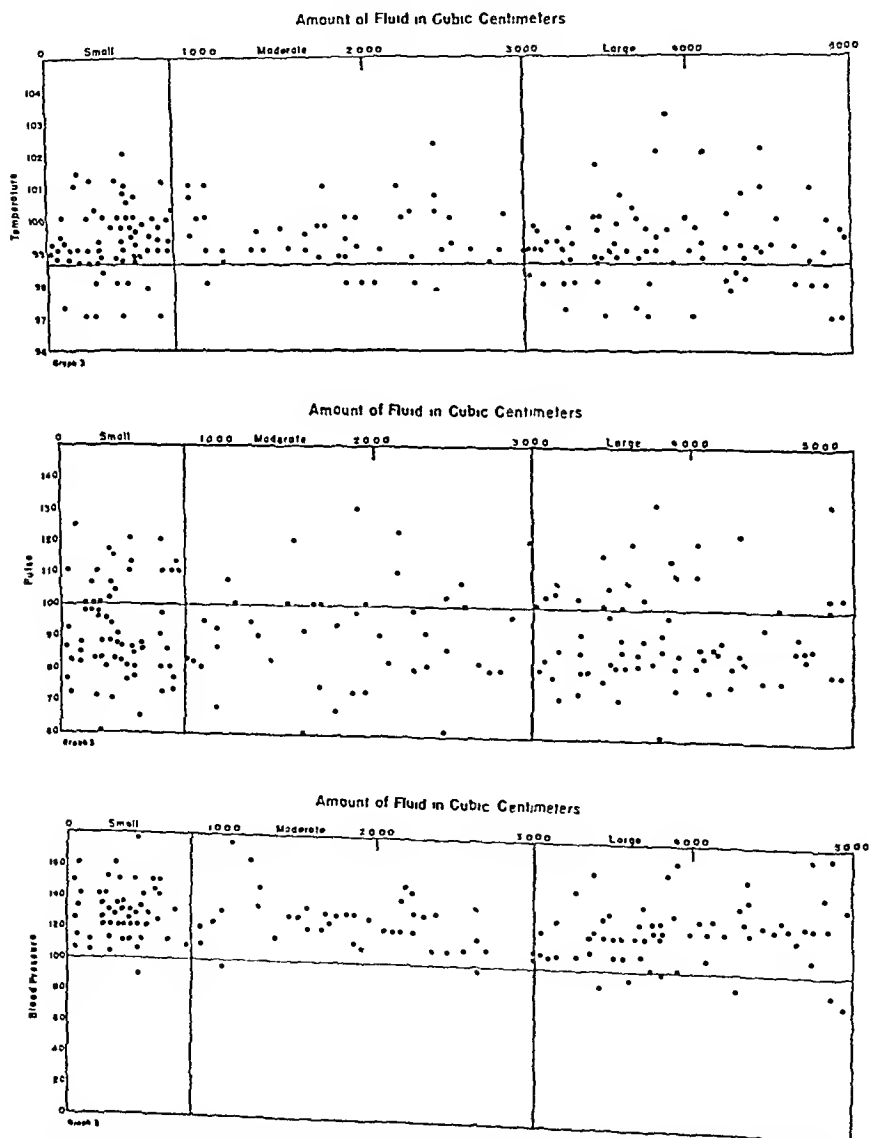


Fig. 3.—In this graph the earliest observed temperature, pulse, and respiration findings are correlated with the amount of fluid found in the peritoneal cavity.

slight in the 2 with complete observations. Although inconclusive, studies on these 16 cases do not lend support to the theory that circulatory collapse always appears immediately after perforation. To illustrate more fully the effect of time on circulatory collapse, the temperatures and pulse and blood pressures of all cases are plotted in Fig. 1 in an effort to give a picture of what is to be found from hour to hour after perforation. There are obviously more high temperatures in the cases of twenty-four or more hours' duration, but subnormal temperatures can be found at any time and there are some high temperatures

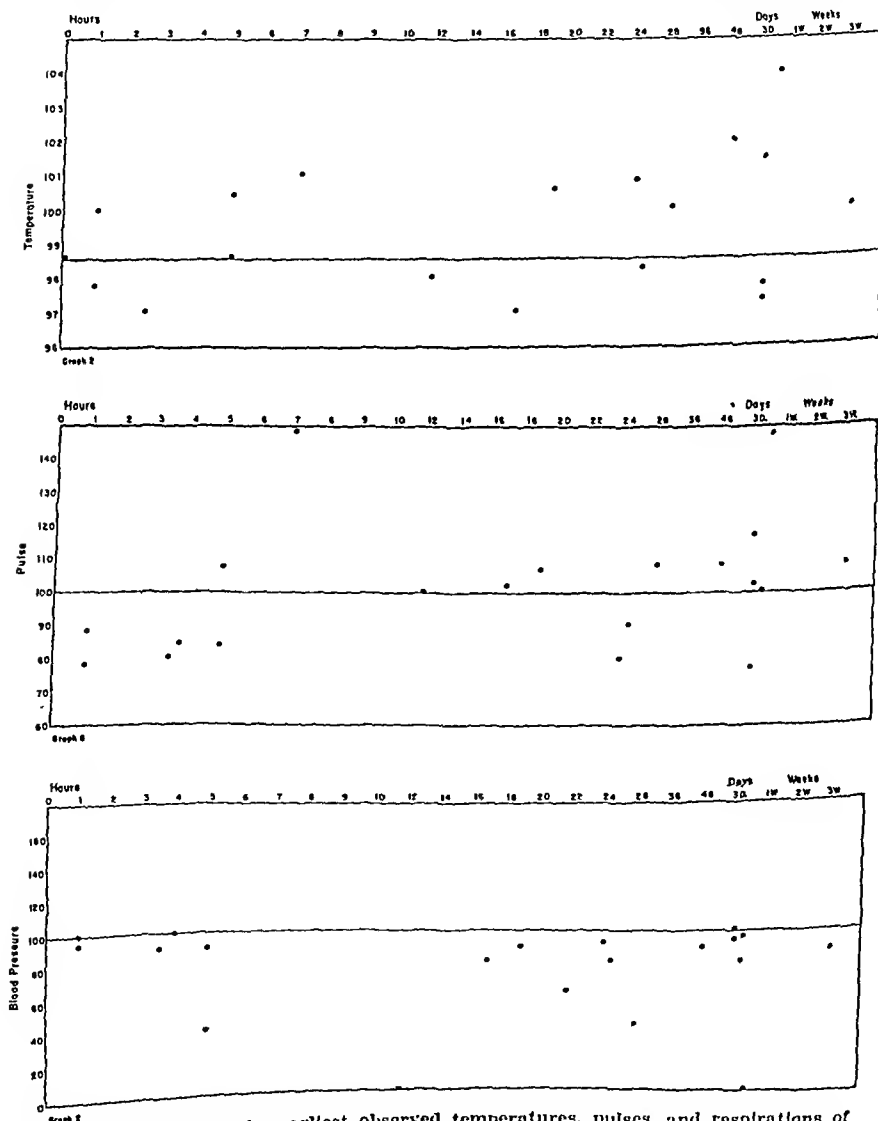


Fig. 2.—In this graph the earliest observed temperatures, pulses, and respirations of the twenty cases in mild or severe shock are represented by dots.

## RELATIONSHIP OF SHOCK TO AMOUNT OF FLUID AND SIZE OF ULCER

The correlation between amount of fluid in the peritoneal cavity and signs of shock is plotted in a similar manner in Fig. 3, but the effects of time, infection, and intercurrent disease have been eliminated, and only uncomplicated cases examined within the first twelve hours of the disease

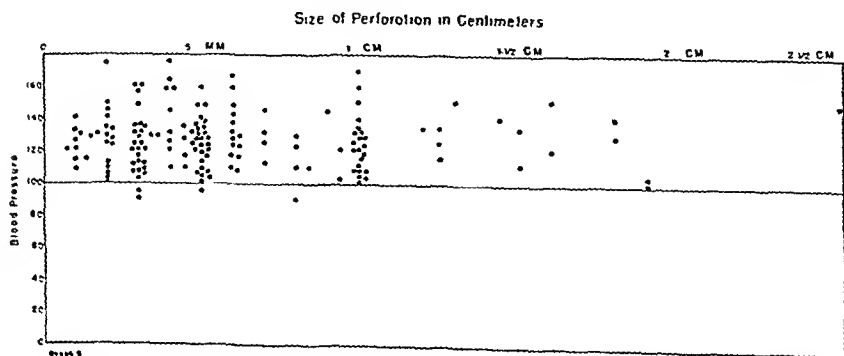
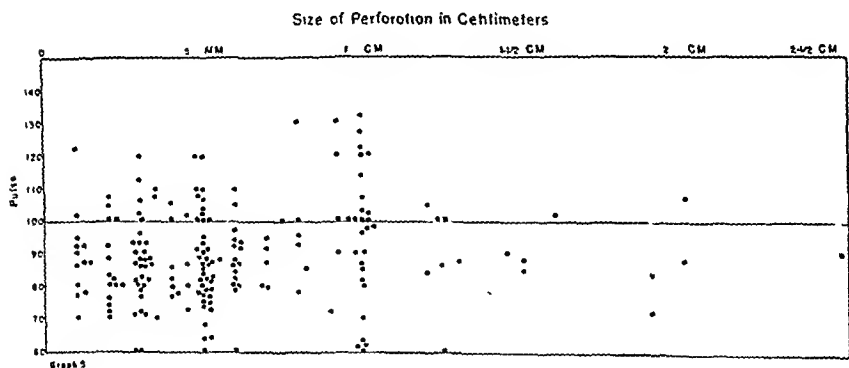
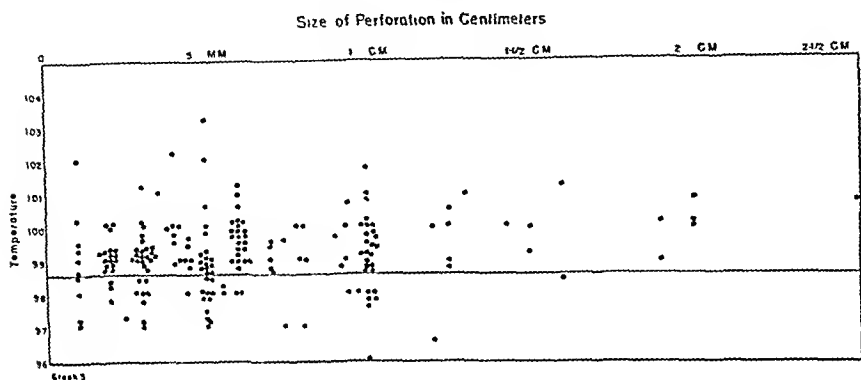


Fig. 5.—In this graph the earliest temperature, pulse, and respiration observations are correlated with the size of perforation in centimeters.



their duration of symptoms. One case was omitted because of the uncertain time of onset. There are obviously more late than early cases here, 10 of them being over twenty-four hours, but enough early cases (Fig. 1) so that one cannot say that there is any definite period in which signs of shock are more apt to be found, nor that there is a very marked preponderance of late cases over early, or vice versa.

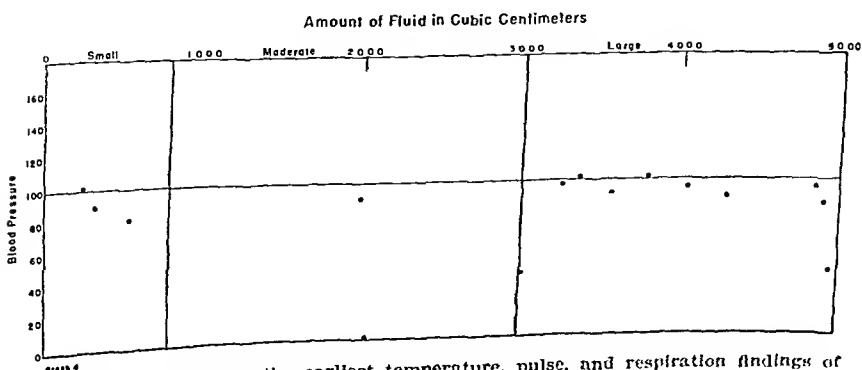
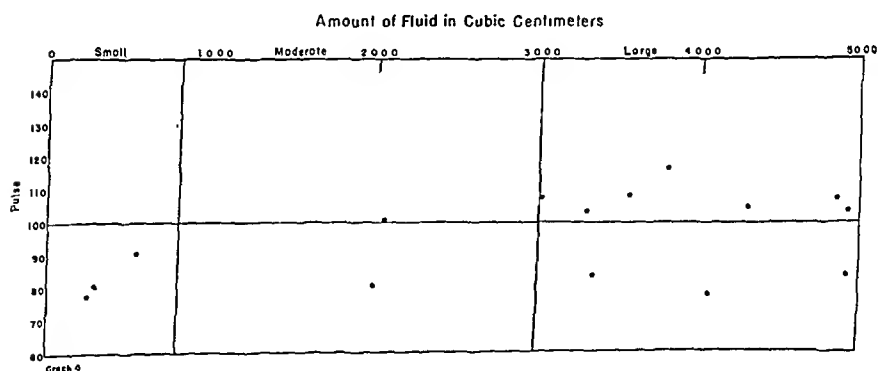
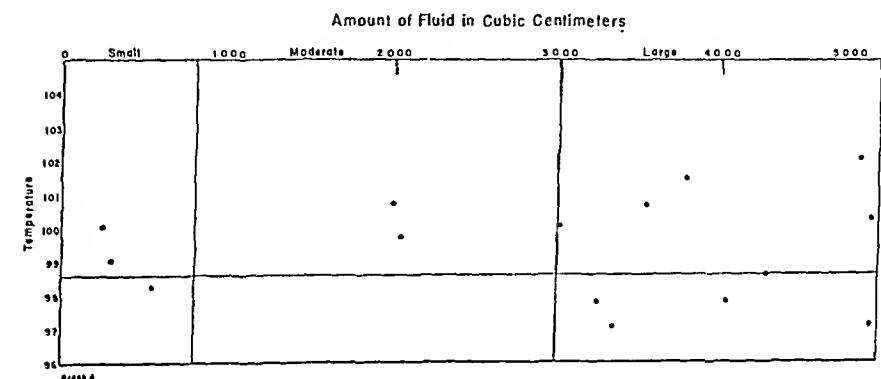


Fig. 4.—In this graph the earliest temperature, pulse, and respiration findings of the group of cases in mild or severe shock are correlated with their peritoneal fluid content.

Fallis' figures of 26 per cent.<sup>9</sup> These signs were found to occur at any time during the disease, neither preponderantly early nor late. They were not dependent upon the size of the perforation or the amount of fluid. If they were present, a cause other than perforation was found in four-fifths of the cases, particularly in the late ones in which it was peritonitis. The treatment was for shock as well as for the underlying disease and the outlook was grave, particularly in the late cases in which signs of shock were synonymous with infection and a consistent prelude to death.

I wish to express especial thanks to Dr. J. A. McCreery, Dr. G. S. Dudley, Dr. A. M. Wright and Dr. C. G. Burdick for the use of their records for this paper.

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are included. Again, with the single exception of a few more lower blood pressures in the group with exudates over 3,000 c.c., there are no significant differences between the groups, and there seems to be no relationship between the amount of peritoneal contents and shock. In Fig. 4 those cases in the group of 20 in mild or severe shock in which the amount of peritoneal content was noted are plotted regardless of time, bleeding, or signs of infection. Here there is a definite preponderance of cases with large exudates, but, as one-fifth of these patients had small exudates, it is difficult to say that any real emphasis can be laid on the point. Fig. 5 correlates the size of the ulcer with signs of shock. In this figure, as in Fig. 3, the cases used were in their first twelve hours and were without intercurrent disease. This heart is made separately from the fluid one, due to the fact that some large ulcers exist with small exudates, and vice versa. Here, again, the findings do not point to increased signs of shock in either the large or the small ulcers.

#### DIAGNOSIS, THERAPY, AND PROGNOSIS

The signs of shock in perforated ulcer are so infrequent as to be of little value diagnostically. However, because of their association with complicating factors, such as infection, hemorrhage, etc., and their relatively rare existence without a complicating factor (only 20 per cent of the group of shocked cases listed above were without one) when some or all signs of shock are present, peritonitis should be suspected in the late cases and hemorrhage, cardiac failure, and early peritonitis in the early ones. Treatment of the signs of shock in most instances rests on the treatment of the complicating factor, independent of the perforation. Treatment of the latter alone cannot be expected to dispose of them. In the ordinary case of perforated ulcer without dehydration, operation need not be delayed for administration of fluids, both because time is a vital factor and because the circulatory system ordinarily is not so affected by the disease as to require preoperative administration. Prognostically, the signs of shock are of some significance. The mortality in the 20 cases of mild and severe shock was 85 per cent. Among the 4 cases in which the responsibility for their condition could be laid at the door of the perforation alone, it was 25 per cent. In the 3 cases of full-blown circulatory collapse, it was 100 per cent. Of even more significance is the effect of these signs in the group of cases of twenty-four hours or more duration. Sixty-eight patients out of the whole series of 335 entered twenty-four hours after the onset of symptoms. They had a mortality of 43, or about 63 per cent. Omitting the 10 cases showing mild or severe signs of shock, the mortality for the remaining 58 was 57 per cent, while for the shocked ones it was 100 per cent.

#### SUMMARY

In conclusion, out of a series of 335 cases, there was profound shock in but 3, and mild signs in 17 more, a total of 6 per cent, as compared with

"Differentiation roentgenologically, of benign tumors and other gastric lesions can seldom be absolute, but in many instances the roentgenologic signs warrant an attempt at such a distinction."

Lipoma of the stomach originates either from the submucous or subserous portion of the wall. The tumor may vary in size from a pea to the size of an orange. It may project into the lumen of the stomach or may project outward, producing very little deformity of the inner contour of the stomach. The position of this tumor is quite variable, but frequently it occurs near the pyloric ring producing obstructive symptoms. One side of the tumor may be covered with mucosa which may show some ulcerations and erosion. It is this latter complication which usually produces the symptoms which bring the patient to the physician. Grossly and microscopically the tissue of the lipoma has a soft, greasy characteristic lobulated appearance not unlike lipomas found elsewhere in the body.

The pathogenesis of benign tumors has been ascribed to several factors. Some authors suggest that these tumors are congenital in origin, arising from some anlage separated during early fetal life. This theory would explain the familial tendency that is sometimes observed as in my case report. Others maintain that chronic irritation, either chemical or physical, gives rise to low-grade inflammatory disorders of the stomach wall. However, against this theory, microscopic examination reveals tumors arising from normal gastric mucosa. Chronic gastritis is often seen with no evidence of microscopic metaplasia.

Minnes and Geschicter<sup>2</sup> conclude that "although chronic irritation and chronic inflammation may be contributing factors in the production of gastric tumors, they are by no means essentially etiologic agents."

Since 1835 we have been able to find thirty-five cases of submucous lipomas of the stomach reported. An additional case is here recorded. (Table I.)

#### CASE REPORT

S. W., white female, 47 years of age, entered the hospital Oct. 8, 1939, complaining of "ptomaine poisoning." Two days before admission to the hospital she had eaten some corned beef and later in the evening went for an automobile ride. After riding about an hour she suddenly experienced a "sinking feeling" and then vomited a small amount of blood. As she returned home and as she was getting out of the car she again vomited and in the vomitus was about one half pint of blood. The following morning her stools were coal black and tarry. She grew much weaker and was sent to the hospital for further study.

The patient's past history was essentially negative for indigestion and hematemesis or black stools. She stated, however, that four years before she had become suddenly weak and quite anemic and had been given a tonic containing iron with improvement of her symptoms. Her habits have been very moderate. She has had no other illnesses.

Her family history is essentially negative except that she has a brother, sister, and two nephews who have had lipomas removed from their extremities.

## SUBMUCOUS LIPOMAS OF THE STOMACH

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*(From the University of Kansas Hospitals)*

**S**UBMUCOUS lipoma is the most uncommon of the benign tumors of the stomach. Less than 1 per cent of all tumors of the stomach are benign and only about 3 per cent of the benign tumors are lipomas. These tumors are frequently confused clinically and radiographically with malignant and inflammatory lesions. Because of their size, position, and complications, gastric function may be so disturbed that surgical removal becomes imperative. When these tumors are pedunculated, they may prolapse into the pylorus and produce the symptoms of pyloric obstruction and later the tumor may fall back into the stomach, producing a quiescent period free from symptoms. Gastric lipomas may be present without ever having produced symptoms and may be found only at autopsy.

One of the most common and significant symptoms of all benign tumors of the stomach is anemia and weakness due to recurring hemorrhage as a result of ulceration or erosion of a portion of the tumor.

Loss of weight, emaciation, epigastric pains, anorexia, nausea, vomiting, hematemesis and melena are all suggestive symptoms but are by no means diagnostic.

The roentgenologic findings are fairly characteristic, and, according to Moore,<sup>1</sup> benign tumors present certain roentgenologic signs which differentiate them from malignant or inflammatory lesions. He says:

"If these signs are not characteristic, they are at least suggestive:

"1. They produce a filling defect that is circumscribed and punched-out in appearance.

"2. The filling defect is usually on the gastric walls, leaving the curvature regular and pliant.

"3. While the rugae are obliterated in the immediate area of the tumor, just as in inflammatory and malignant lesions, the rugae surrounding a benign tumor are more nearly normal in their arrangement and distribution.

"4. They cause little or no disturbance in peristalsis, and retention is uncommon except when the lesion is at, or very near, the pylorus.

"5. They do not reveal a niche, nor is there any incisura or other evidence of spasm.

"6. They are rarely sufficiently large to be palpated.

"Probably the most essential feature in the examination is the close and complete approximation of the walls of the barium-filled stomach. . .

TABLE II—CONT'D

CASE	YEAR	AUTHOR	SEX	AGE	DISCOVERY	SIZE	CLINICAL FEATURES
20.	1931	Comfort	F	65	Autopsy	8 mm. diameter	
21.	1931	Comfort	M	74	Autopsy	1 by 2 by 3.5 cm.	
22.	1933	Mundl and Vogl	M	43	Excision	Pedicle tumor, larger than a nut	Ulcer history
23.	1933	Pansdorf and Determann	F	65	Resection	Broad-based; 1 cm. in diameter	Weber's test positive in feces; roentgen, benign tumor
24.	1934	Melchior	M	57	Resection	Oscillating tumor, size of cherry	Weber's test positive; symptoms simulating cholecystitis
25.	1934	Santy	F	40	Resection	Tangerine	Anemia, pains after food, vomiting, Weber's test in feces positive
26.	1935	Glass	M	30	Resection	Broadbased tumor, size of fist	Epigastric pain, black stool, Weber's test positive in feces
27.	1935	Kirschbaum	F	75	Autopsy		
28.	1935	Troisier			Autopsy	10 tumors, largest size almond	Anemia profuse hemorrhage
29.	1936	Kantorovitch	F	29	Resection	Size of kidney	Nausea and vomiting, roentgen ray showed benign tumor
30.	1937	Métivet	M	69	Resection	20 cm. in diameter	Blood in stools, roentgen ray showed probably benign tumor
31.	1938	Redell	F	33	Resection	167 Gm., twice the size of hen's egg	Black stools, Hb. 31 per cent, Weber's test in feces positive
32.	1938	Garre, Garelik, and Ciarlo	M	50	Resection	9 by 4 cm.	Eruetations, abundant hematemesis
33.	1940	Rumold	F	47	Resection	7.5 by 5.5 by 5 cm.	Eruetations, nausea, vomiting, blood in stools, anemia

On physical examination the patient was a well-developed, white, rather anemic appearing, female weighing about 150 pounds. Her hair was entirely white. She had no discomfort. Examinations of the head and chest were essentially negative. The blood pressure was 130 systolic and 70 diastolic. Pulse rate was 84 per minute and was regular. Examination of the abdomen revealed a tenderness in the mid-epigastrium, but no definite mass could be palpated. Extremities were normal. Reflexes were within normal limits.

TABLE I  
TABULATION OF GASTRIC LIPOMAS REPORTED IN THE LITERATURE

CASE	YEAR	AUTHOR	SEX	AGE	DISCOVERY	SIZE	CLINICAL FEATURES
1.	1835-1842	Cruveilhier			Autopsy	Almond	
2.	1863	Virchow	M		Autopsy	Hazelnut	
3.	1889	Murray		64	Autopsy		
4.	1893	Tilger		High age	Autopsy	Hazelnut	
5.	1893	Tilger		High age	Autopsy	Hazelnut	
6.	1905	Bénaky	M	65	Autopsy	6 by 3, 5 by 2 cm.	
7.	1905	Fischer	F	37	Resection	Walnut	Pains in umbilical region; gastric juice normal
8.	1905	Hellstrom	M	77	Autopsy	Hazelnut	Free from symptoms
9.	1911	Westenhoeffer			Autopsy		
10.	1912	Randisi	M	65	Resection	Triangular prismatic tumor	Epigastric pains, vomiting, emaciation, 28 mo. duration.
11.	1922	Verger and Massias	F	58	Autopsy	Hazelnut	Anorexia, nausea, diarrhea, emaciation, cachexia
12.	1924	Nahmmacher	F	65	Autopsy	8 by 3, 5 by 3 cm.	
13.	1925	Eliason and Wright	M	52	Autopsy	Solitary tumor in fundus	
14.	1926	Bianchi	F	57	Autopsy		Vomiting for 12 mo.
15.	1926	Spitzmuller	M	69	Resection	Tangerine	Palpable tumor, blood in stools, vomiting, pain after meals
16.	1928	Weicker	M	60	Resection	Small apple	Pains after meals, sometimes vomiting, achylia, x-ray defect, fatigue, emaciation
17.	1929	White and Judd	F	59	Resection	5.5 by 3 5 by 2.3 cm.	Attacks of fatigue, x-ray defect, hemorrhage, tarry motions
18.	1930	Neumann	F	62	Resection	15 by 4 cm.	Mild eructations, x-ray reveals tumor in pars cardiaca
19.	1931	Comfort	M	67	Autopsy	9.5 by 4.5 cm.	

The clinical diagnosis was a gastric polyp showing probably beginning malignancy since ulceration and hemorrhage were present.

Before operation the patient was given three blood transfusions of 500 c.c. of citrated blood each, bringing her hemoglobin up to 84 per cent.

Four days after admission into the hospital the patient's abdomen was explored. Cyclopropane and spinal anesthesia were used. Attached to the posterior wall of the stomach was a soft tumor mass measuring about 6 cm. in diameter which projected into the lumen of the stomach. There were no masses in the liver and gastrohepatic lymph glands were not enlarged. A sleeve type of resection was done which included the tumor mass. (Fig. 2.)

The patient's postoperative course was uneventful. She was dismissed on the twenty-first postoperative day free of symptoms.

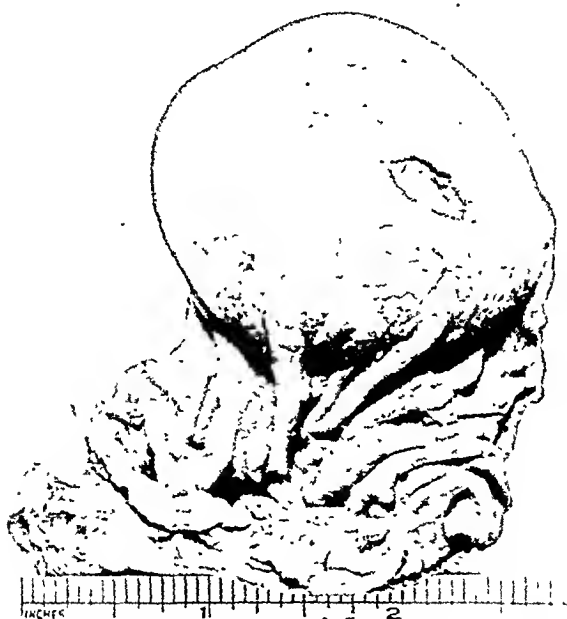


Fig. 2.—Gross appearance of the lipoma showing ulceration.

The pathologist's report was as follows:

"The specimen consists of a portion of the stomach which has been removed by sleeve resection and measures 5 cm. in width and 4.5 cm. in diameter. The entire specimen weighs 110 grams. Arising from the region of the submucosa there is a pedunculated growth which projects into the lumen of the stomach and measures 7.5 by 5.5 cm. The wall of the stomach is not thickened and the mucosa shows the normal pattern of the rugae except over the pedunculated growth. Here it becomes flattened out and atrophic in appearance. In one area there is a craterlike ulcer which measures 1.5 by 0.7 by 0.4 cm. and several other small areas of superficial erosion measuring from 1 to 2 mm. in diameter. The floor of the larger ulcer is rough and covered with a shaggy gray exudate.

"A section through the mass shows it to be composed of a light yellowish greasy tissue which contains a few strands of white fibrous tissue. No definite lobulation is demonstrated. The picture is that of a pedunculated intragastric lipoma arising from the submucosal coat.



Laboratory examination revealed a red blood cell count of 3,200,000 with a 51 per cent hemoglobin. The white cell count was 6,000 with 63 per cent polymorphonuclear leucocytes. The blood nonprotein nitrogen was 27.4 mg. per cent; creatinine, 1.3 mg. per cent; sugar, 84 mg. per cent; and chloride, 530 mg. per cent. Wassermann and Kahn tests and urinalysis were negative. The stool examination showed occult blood. There was no free hydrochloric acid in the stomach.

Roentgenologic examination of the stomach was reported as follows:

"The stomach is of average size. In the body of the stomach approximately halfway between the pylorus and esophageal orifice we see a circular filling defect measuring approximately 2.5 inches in diameter [Fig. 1]. By manipulation we can determine that this arises from the posterior wall of the stomach. A mass cannot



Fig. 1.—Roentgenogram showing a defect at the site of the lipoma in the barium-filled stomach.

be felt here because the area is not accessible to palpation. Subsequent injection of thick barium to visualize mucosal detail shows a wiping out of detail of the mucosal shadows particularly in the medial portion of this filling defect. We are unable to move the filling defect about; it constantly maintains its position. In conclusion there is a soft tissue mass in the body of the stomach arising from the posterior wall producing a smooth filling defect. While it is conceivable that this may be a benign polyp because of its smooth outline, we must consider it malignant until proved otherwise.

"Re-examination of the stomach twenty-four hours later shows the peculiar large filling defect in the body of the stomach as previously described. Its position has not changed."

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"Microscopic sections through the stomach wall adjacent to the tumor show nothing unusual. The stroma of the mucosa is in fields slightly increased in amount and somewhat edematous. An abundance of monocytic cells, many of which are plasma cells are frequently seen. A few small foci of lymphocytes are noted near the muscularis. The glands are well preserved and show both chief and parietal cells. In many fields the capillaries are congested and contain an occasional polymorphonuclear leucocyte.

"Another section through the mucosa taken over the growth shows the mucosa to be somewhat thinned out and atrophic in appearance. The branching gastric glands are much shorter than usual and surrounded by an increased amount of fibrous tissue. There is also some round-cell infiltration with small foci of lymphocytes and many plasma and eosinophilic cells. Some areas of edema and slight congestion of the blood vessels are also noted. In some fields toward the outer surface of the mucosa the epithelium has been desquamated leaving a raw fibrous surface. This, however, is not marked and very little catarrhal reaction or inflammatory reaction is seen."

The pathologic diagnosis was an unusually large pedunculated, intragastric submucosal lipoma showing ulceration and superficial erosion.

#### SUMMARY

A review of the literature now reveals a total of 33 cases of submucous lipoma of the stomach reported since 1835; of these, 17 were found at autopsy and 16 were resected at operation. The size of these tumors was reported to vary from that of a pea to that of an orange. Sex incidence was found to be equal. Age incidence varied from 29 to 84 years. Anorexia, nausea, vomiting, hematemesis, and melena were not uncommon symptoms associated with these tumors. Since there is nothing really pathognomonic in the symptomatology, the diagnosis of submucous lipoma of the stomach is rarely made before operation. However, a careful roentgenologic examination may lead one to suspect such a tumor. If the presence of a benign tumor is suspected, an exploratory operation and removal of the tumor with its involved stomach wall are indicated. Removal of the stomach wall is necessary since there have been reported cases of recurrences where only the tumor was removed.

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extent in the remainder of the intestine. The blood also remained a fluid longer than normal and the dried weight of the blood was above normal. They found that death resulted also if the injection was made intraperitoneally or subcutaneously. They found that blood from a dog with a closed duodenal loop did not produce toxic symptoms when injected intravenously into another dog and this was true even when the dog had died from the obstruction. The intestinal content was found to produce no symptoms when injected into the lumen of the intestine of the normal dog. These investigators thought from their studies that the dogs showed some immunity on repeated intravenous injections of the fluid and that dogs thus immunized could survive a closed loop twice as long as an unimmunized dog (four days instead of two). From the protocols of the experiment, however, there seemed to be so much variation in the length of life that this particular work does not seem to us to be conclusive.

Whipple, Rodenbaugh, and Kilgore<sup>58</sup> attempted to purify the toxic material from an obstructed loop by precipitation with alcohol, centrifugalization, and heating to remove the albumin, and apparently after this procedure the toxic material was more concentrated. It produced on intravenous injection, diarrhea, vomiting, lowered blood pressure, rise in urinary nitrogen, and an excess of antithrombin with incoagulable blood. They believed that their method of purification removed practically all substances except primary proteoses, and they believed that they were dealing with a heteroproteose because it resisted pancreatic digestion.

Murphy and Vincent,<sup>49</sup> in 1911, found the material from an obstructed intestine to be poisonous when injected intraperitoneally, but the poisonous properties were destroyed by boiling or by passage through a Berkefeld filter, and they concluded that bacteria were responsible for the toxin. Von Baracz<sup>57</sup> found that dogs with a closed ileal or cecal loop might live for many weeks. Hartwell and Hoguet<sup>50</sup> found that the length of life with high intestinal obstruction was not related to the amount of food in the intestine above the obstruction. Hartwell<sup>50</sup> later concluded that the length of life is inversely proportional to the amount of mucosal damage. Roger,<sup>51</sup> in 1907, found that the normal contents of both stomach and intestine were toxic when injected without filtration intravenously into a dog. Other investigators, including Whipple and his co-workers,<sup>59</sup> did not agree with this finding. McClintock and Hines,<sup>45</sup> however, scraped the mucosa and the intestinal contents from the entire small intestine of a normal dog, concentrated it by Whipple's method, and found that this material sometimes killed the injected dog; but, if the material from four dogs was used, it always killed the injected dog. The blood of the injected dog showed a rise of nonprotein nitrogen, concentration of cells, and sometimes a decrease in chlorides. These workers also obtained a lethal dose by scraping the mucosa from

## THE TOXICITY OF INTESTINAL CONTENT AND OF THE TRANSUDATE FROM AN OBSTRUCTED LOOP

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THE question of the toxicity of intestinal contents injected intravenously and the relation of such toxicity to intestinal obstruction with its train of symptoms has never been entirely clarified. The idea that death in intestinal obstruction is due to decomposition or stagnation of the intestinal content was first suggested by Amussat<sup>1</sup> in 1839. Kocher,<sup>43</sup> in 1877, concluded from experiments on rabbits that, since peritonitis was not present, death must be due to intoxication, and he demonstrated that the condition of a patient with intestinal obstruction could be improved by enterostomy or by removal of the intestinal content. Kirstein,<sup>40</sup> in 1899, injected the contents of obstructed intestinal loops intravenously into rabbits and produced gastroenteritis, collapse, and death within a short time. A similar picture was produced by such injections into cats. Gley and LeBas<sup>23</sup> brought up the question of whether or not this toxic substance present in the lumen of an obstructed intestine might be a proteose, but, since the injection of a proteose caused an increased lymph flow and the toxic substance apparently did not, they decided against its being a proteose. Chittenden, Mendel, and Henderson<sup>6</sup> in 1898 studied the effect of proteose injections and found that the coagulation time of the blood was reduced. Chittenden also reported that proteoses and peptones caused a fall in blood pressure and a disintegration of the leucocytes.

About 1910 Whipple, Stone, and Bernheim<sup>59</sup> began a very intensive study of the question of the nature of the toxic substance in intestinal obstruction. They produced a closed loop by isolating the duodenum with ligatures from just below the pancreatic duct to the duodenojejunal junction. The ligatures were buried with mattress sutures and the continuity of the gastrointestinal tract was re-established by gastroenterostomy. They found that, if they washed out the contents of such a loop before an obstruction was produced, the dogs lived one to three days as compared to one to two days with the unwashed loop. The fluid content from an obstructed loop was autolyzed for ten days at 38° C. between toluol and chloroform. It was then heated to between 60 and 70° C. for one-half to one hour and centrifuged, the supernatant fluid being filtered through a Gooch crucible. Forty cubic centimeters of this material was injected intravenously into dogs and the animals passed bloody mucus and died in about four hours. At necropsy the duodenum was swollen and purple, and this color was also visible to a lesser

loops were found to contain thick, gray material, a small amount of which injected intravenously would kill another dog.

Dragstedt and his co-workers<sup>12</sup> made closed intestinal loops, strained the contents, and heated it for one hour over a water bath at 70° C. The coagulum which formed was filtered off, and the filtrate, which was toxic, was kept between toluol and chloroform at room temperature. They found no evidence of anaphylaxis on injection of this material, and stated that normal intestinal content which Davis and Stone found to be nontoxic becomes toxic after standing unpreserved. Dragstedt and his co-workers<sup>12</sup> concluded that the toxic substances in a closed loop are probably not protein in nature.

Dragstedt (L. R.), Dragstedt (C. A.), McClintock, and Chase<sup>15</sup> made closed loops of duodenum or upper jejunum which had been previously washed with sterile water and ether. They found that about one-half the animals survived indefinitely. The loops, however, were found to contain many bacteria and the contents of such loops were found to be toxic when injected intravenously or intraperitoneally. They tried washing the loops with other substances (alcohol, phenol, lysol, formaldehyde, mercuric chloride, silver nitrate, chloroform, and cresol) but none of these were as effective as ether. They believed that ether prevented the absorption of toxic substances or depressed the intestinal secretion. Washing the loop with an astringent (8 per cent aluminum potassium sulfate) had the same effect as ether and 6 per cent tannic acid was also very satisfactory. If a long (six feet) ether-washed loop was made, the dogs remained well for two weeks and then a slowly developing toxemia appeared.

Dragstedt, Moorhead, and Bureky<sup>17</sup> isolated a loop of duodenum or jejunum, re-established the intestinal continuity, and dropped the open loop back into the abdominal cavity. At reoperation the ends of the loop were found to be closed by adhesions and the loop was distended with thick yellow fluid which was sterile. Dragstedt and Moorhead,<sup>13</sup> in further studies made on these open loops, found that the lower down in the intestinal tract the loop was made, the less chance there was of the dog surviving. About one-half the loops remained open and the other half were closed by omental adhesions. They found that when a closed loop was made and removed in time to save the animals' lives, no immunity developed to subsequent injections or obstructive operations.

Cooke, Rodenbaugh, and Whipple<sup>7</sup> found that there was a rise in the noncoagulable nitrogen, urea nitrogen, amino nitrogen, uric acid nitrogen, creatine nitrogen, and creatinine nitrogen in intestinal obstruction, in closed loops, or after the injection of toxic protease. Haden and Orr,<sup>26</sup> however, found that the changes in the blood produced by the injection of loop contents were not so marked as those found by Whipple. They also found no definite change in the chlorides even with a pronounced rise in nonprotein nitrogen. The injection of Witte's peptone,

the intestine of a man who died from Hodgkin's disease, and Ellis<sup>19</sup> obtained it from dogs with portal thrombosis. Sweet, Peet, and Hendrix<sup>56</sup> believed that the only cause of death in dogs with a closed intestinal loop is distention and rupture of the loop. They found, as did previous workers, that a closed loop of the lower ileum was tolerated for long periods but that, if such a loop were made and filled with pancreatic juice or pieces of pancreas, the animal died as in high obstruction. They ligated the pancreatic ducts in three dogs and these animals lived for seven or eight days with a high obstruction. They obtained a toxic material from the intestine of these dogs, but they concluded that it was not a proteose and believed that the symptoms suggested choline bases as the toxic factor. They suggested that the symptoms of pancreatitis are due to intoxication with products of protein cleavage and that this is true also in intestinal obstruction. Raine and Perry<sup>50</sup> placed rubber tubes around the bowel and brought the ends of the rubber tubes out through the skin, thus producing a closed loop. When the tubes were tightened, the intestine was obstructed and the animals quickly developed symptoms, but when the tension was released, they quickly recovered and the blood chlorides soon returned to normal. This experiment, however, is complicated by the fact that they were dealing with not only a closed loop, but also an intestinal obstruction above the loop.

Murphy and Brooks<sup>48</sup> concluded that the toxicity of the material in an obstructed loop was decreased by prolonged autolysis or by passing through a Berkefeld filter. They also made a 20 cm. loop of jejunum, which was drained to the outside through a stab wound, and the dog was followed for five months. When the loop was closed by operation or by contracture of the stoma, the dog became sick, but it recovered as soon as drainage was established. Murphy and Brooks found that the thoracic duct fluid from a dog with a closed loop was not toxic but believed that they had demonstrated toxicity in lymph from the thoracic duct of a dog which had a closed loop and in which the loop was further distended by the injection of more loop contents from another dog. They also found that the contents of a gangrenous gall bladder were not toxic, but, if intestinal content was put into the gall bladder before gangrene was produced, the gall bladder fluid did become toxic.

Burget and his co-workers,<sup>4, 5</sup> made closed loops of ileum or jejunum which they placed under the skin. They found that distention of these loops was accompanied by vomiting but that the dogs could be kept alive indefinitely by tapping the loops and relieving the pressure.

Brooks, Sehnmacher, and Wattenberg<sup>3</sup> made 80 cm. closed jejunal loops and sutured the ends carefully to produce the least possible mucosal damage. They re-established the continuity of the intestinal tract and the dogs lived as long as three weeks. They gave the protocol on one dog, but said that it was typical of many similar cases. The

in 1923, pointed out the drop in blood chlorides and showed that dogs could be kept alive by the injection of normal saline solution. Dragstedt and Ellis<sup>14</sup> showed that the loss of gastric juice from isolated stomach pouches caused dehydration, alkalosis, and death. Gamble and McIver<sup>22</sup> and Elman and Hartmann<sup>20</sup> showed that pancreatic fistula caused death by dehydration and acidosis. Elman and Hartmann<sup>20</sup> believed that the cause of death in obstruction or fistula high in the intestine is due to the loss of the gastrointestinal secretions and subsequent change in body fluids, but they do not believe that death in low obstruction is caused by this means. Hartwell, Hoguet, and Beekman<sup>32</sup> believe that there is no toxemia in intestinal obstruction, except that produced by the loss of water, unless the intestinal wall is damaged. Haden and Orr<sup>25</sup> investigated the effect of other inorganic salts in prolonging the life of dogs with high intestinal obstruction. They found no beneficial effect from potassium chloride, calcium chloride, or magnesium chloride. Sodium bromide apparently did some good but was not as effective as sodium chloride. Iodides, on the other hand, seemed to hasten the toxic process.

Haerem, Dack, and Dragstedt<sup>27</sup> placed *Cl. botulinum* toxin in the closed intestinal loop of a dog and the greatest amount was found in the blood on the fourth day. After x-ray studies of the loops, the authors believed that there was some correlation between absorption of the toxin and distention of the loops.

Morton and Sullivan<sup>47</sup> made 10 cm. closed loops of duodenum and ileum in the same dog. The animals were anesthetized every twenty-four hours and the contents were aspirated with a needle, measured, and returned to the loop. The amount of secretion in the ileum was found to be very small (1 c.e. in seventy-two hours) but in the duodenum averaged 11.3 c.e. the first twenty-four hours, and 35.7 c.e. total at forty-eight hours. The intraloop pressure measured with a manometer was found to be four to seven times as great in the duodenum as in the ileum. They also noted a fall in blood chlorides and a rise in nonprotein nitrogen. Sperling<sup>55</sup> found that an obstructed bowel cannot absorb as much water as a normal bowel. An increase of intraintestinal pressure results in the gradual increase of water absorption until a pressure of 40 c.e. of water is reached, then absorption decreases and stops at 75 mm. of mercury pressure. They found that strychnine does not pass through the wall of a devascularized bowel unless the pressure is increased. They also found a slight but definite delay in the absorption of strychnine from the obstructed bowel.

South and Hardt<sup>54</sup> placed a closed loop extraperitoneally under the skin with re-establishment of the intestinal continuity. They found that a toxemia developed but was relieved when the loop perforated. If they washed out the loop with normal saline solution, they thought the life of the dogs was somewhat prolonged. Eisberg<sup>15</sup> placed a similar closed loop between the fascial planes of the abdomen wall but



which contains mainly proteoses, also caused no significant change in the blood chlorides. Autolyzing liver placed in the abdomen caused an intoxication, but there was no marked change in the chlorides.

Davidson and Mason,<sup>11</sup> however, found that liver, free in the abdomen, did cause a rise in nonprotein nitrogen. Ingvaldsen, Whipple, Bauman, and Smith<sup>37</sup> attempted to determine the chemical nature of the loop contents by an extensive chemical analysis. They concluded that it was a nucleoprotein and that a small amount of histamine was present, but not enough to contribute to the toxicity.

Hibbard and Kremen<sup>33</sup> studied the effect of the volatile base in loop contents and found that it produced toxic symptoms but did not kill the animals. The volatile base-free residue was nontoxic.

Cutter and Pijoan<sup>9</sup> found an increase in the blood potassium in high intestinal obstruction and found that dogs with high obstructions were killed by an injection of 10 c.c. of 1 per cent potassium chloride, which is tolerated by normal dogs. Seudder, Zwemer, and Whipple<sup>53</sup> found a rise in blood potassium in intestinal obstruction and attributed death to this factor. Bisgard, McIntyre, and Osheroff,<sup>2</sup> and Jorgensen, Dietz, and Hill,<sup>39</sup> on the other hand, found no evidence that potassium or change in the sodium-potassium ratio contributed to the cause of death.

Johnstone, Clasen, and Orr<sup>38</sup> found that dogs with the major pancreatic duct transplanted below an obstruction lived three times as long as other dogs with obstructions in the same location. The loss of the bile and pancreatic and duodenal juices is known to cause death (Dragstedt and his co-workers,<sup>16</sup> and Hill, Neigus, and Wilhelmj<sup>35</sup>).

White and Fender<sup>40</sup> kept one dog alive a month, and another two weeks, by giving vomitus below the obstruction through a Witzel enterostomy tube. These authors did not believe that any toxin is formed in nonstrangulated bowel and that chloride neutralizes any toxin. Hill and O'Connell,<sup>34</sup> on the other hand, administered duodenal contents to dogs with high intestinal obstruction and were not able to prolong life.

Cutting<sup>10</sup> found that adrenalectomized rabbits were less able to withstand the injection of loop content than were normal rabbits, and others have directed attention to the similarity in symptoms of intestinal obstruction and bilateral adrenalectomy. Several investigators have considered the possible relationship of *Bacillus welchii* in the causation of toxic symptoms. McIver and his co-workers<sup>46</sup> found no effect from *B. welchii* antitoxin in preventing symptoms of intestinal obstruction in cats with closed loops. Copher, Stone, and Hildreth,<sup>8</sup> on the other hand, found that the antitoxin made dogs with closed loops live an average of 4.6 days compared to 2.3 days in the untreated dogs.

Haerem, Daek, and Wilson<sup>28</sup> were able to demonstrate no evidence of *Clostridium welchii* toxin in loop fluid by injecting this fluid into mice.

Hartwell and Hoguet,<sup>31</sup> in 1912, stated that the cause of death in high intestinal obstruction is the loss of fluid by vomiting. Harden and Orr,<sup>24</sup>

the dogs lived twenty-five hours compared to sixty-six hours without the bag. They considered this demonstrated a striking prevention of toxemia.

The experimental investigations which follow were undertaken in an attempt to provide new light on several of the controversial questions which are apparent in the above review.

#### EXPERIMENTAL METHODS AND RESULTS

*Operative Procedures.*—The operative procedures carried out in this study were all performed under ether anesthesia administered by tracheal intubation after induction in the ether box. No preliminary medication was given. Aseptic precautions were observed in all cases. The abdomen was entered through a midline incision and the jejunum below the suspensory ligament of Treitz was identified with a minimum of trauma. After one of the several procedures described below, the incision was closed in three layers (peritoneum and muscle, subcutaneous tissue, skin) using No. 8 cotton thread as suture material.

**SERIES I, SIMPLE OBSTRUCTION.**—The jejunum was firmly ligated with twilled tape at a point about two feet below the ligament of Treitz.

##### TYPICAL PROTOCOL

Long-haired brown mongrel male (weight 13 lb.)

9/29/39 Obstruction

9/30/39 Stuporous, refuses food

10/ 1/39 Stuporous, takes some water

10/ 2/39 Found dead, 8 A.M.

*Necropsy:* No peritonitis; intestine above ligation moderately dilated; below, moderately collapsed; loop of gut adherent to tie region; mucosa of intestine hemorrhagic; 20 c.c. of reddish brown material with pronounced fecal odor collected from above obstruction.

The material collected from the intestine was filtered through gauze or was concentrated by Whipple's method and injected.

As will be noted in Table I, the results obtained when intestinal contents from an obstructed bowel were injected intravenously varied considerably. There seemed to be no relationship between the amount of material injected and the effect produced and no increased effect was obtained by concentrating the material according to Whipple's method. In fact, in this series, the concentrated material was apparently less toxic than the untreated contents.

**SERIES II, NORMAL INTESTINE.**—In this series intestinal content was obtained from dogs which had been sacrificed in some other investigative work. The contents were obtained shortly after death and were milked out of the upper intestine. The material was strained through gauze and immediately injected intravenously into a healthy dog.

*Comment.*—In general the effect produced by normal intestinal content was at least as pronounced as that obtained by the injection of the contents of obstructed bowel.

found that this did not prolong life. When the loop was placed outside the skin, the animal lived and was not affected. When the loop was inside the abdomen or in the abdominal wall, the dog died in seventy-two hours.

Scott<sup>52</sup> made strangulated loops with and without ligature of the arteries. He found that the weight of the strangulated intestine increased from 133 to 490 per cent. Peritoneal fluid was increased and he found that the protein content of this fluid was the same as that of blood. The peritoneal fluid was not toxic when injected intravenously unless the loop had ruptured. Strychnine, histamine, or tetanus toxin was absorbed more slowly than normal from such a strangulated loop. Scott calculated that a strangulated bowel five feet in length would cause a loss of as much as 66 per cent of the total blood volume.

Maycock<sup>44</sup> placed a bag around a loop of strangulated bowel and collected the transudate. When this fluid was injected intravenously, he found an acute depressor effect which he believed was accounted for by the amount of histamine and choline present.

Knight and Slome<sup>42</sup> collected the blood from mesenteric veins draining a strangulated loop, and found a depressor substance present. They also discovered such a substance in lymph from the thoracic duct. They performed cross-circulation experiments in which one animal supplied blood to the strangulation of the entire small intestine of another animal. The donor was not affected by the blood loss and the life of the other animal was not prolonged. Knight<sup>41</sup> found that the release of a strangulated segment of bowel causes 15 per cent mortality in very sick animals due to the release of toxic material in the veins.

Holt<sup>36</sup> found that in strangulation of long loops of intestine (40 cm. or more) over 50 per cent of the blood volume goes into the loop and this is sufficient to cause death in dogs. He found that, when a strangulated loop is put into a rubber bag, life of the animal is not prolonged. He also found that contents of such a loop of twelve hours' duration or the fluid in the peritoneal cavity was not markedly toxic when injected intraperitoneally. The transudate in the bags around the loop was injected intraperitoneally and produced only vomiting, tremor, and weakness when 200 c.c. were injected. He concluded that toxemia is of minor importance in long, strangulated loops, but considers the loss of blood to be the main factor. He placed a strangulated loop 20 cm. long in a bag and drained the bag to the outside. One dog was used and this animal remained well. He concluded that life is prolonged in a dog with a loop of moderate length if absorption of toxin is prevented. He made a previous anastomosis around the loop so that there was no obstruction present.

Foster and Hansler<sup>21</sup> placed a bowel segment in a thin rubber bag and tied a rubber catheter around the base tight enough to obstruct the veins. With loops twenty-four inches long the length of life was not prolonged by use of the bag. When short loops were used (12 inches),

## TYPICAL PROTOCOL

White, smooth-haired mongrel female (weight 26 lb.)

10/23/39 Obstruction

10/24/39 Has not vomited with exception of bile-stained vomitus on recovery from anesthesia

10/25/39 Dog, which appears well, etherized, and necropsy performed

*Necropsy:* No gangrene, no peritonitis; loop enlarged and dilated; 150 c.c. clear, pink fluid collected from bag into beaker containing 4 c.c. of 2 per cent potassium oxalate

TABLE III  
RESULTS IN SERIES III

INJECTED INTO DOG NO.	METHOD OF IN- JECTION	SOURCE: DOG NO.	MATERIAL INJECTED	TIME AFTER OBSTRU- TION PRODUCED	AMOUNT	RESULT
22	Intra- venous	430	Bag contents from obstructed loop	24 hr.; etherized	20 c.c.	No effect
26	Intra- venous	429	Oxalated bag con- tents from ob- structed loop	48 hr.; etherized	50 c.c.	Imperceptible
27	Intra- peritoneal	432	Oxalated bag con- tents from ob- structed loop	72 hr.; etherized	50 c.c.	Immediate vio- lent reaction; several days diarrhea; ulti- mate recovery
28	Intra- venous	431	Oxalated bag con- tents from ob- structed loop	48 hr.; etherized	50 c.c.	No physical signs
29	Intra- peritoneal	436	Oxalated bag con- tents from ob- structed loop	72 hr.; etherized	30 c.c.	No reaction
30	Intra- peritoneal	434	Bag contents from obstructed loop	72 hr.; etherized	48 c.c.	No effect
31	Intra- peritoneal	440	Bag contents from obstructed loop	72 hr.; etherized	100 c.c.	Slight discom- fort which dis- appeared
33	Intra- venous	441	Bag contents from obstructed loop	72 hr.; etherized	15 c.c.	No physical symptoms
35	Intra- venous	443	Oxalated bag con- tents of ob- structed loop	72 hr.	40 c.c.	No reaction
36	Intra- venous	444	Oxalated bag con- tents of ob- structed loop	96 hr.	50 c.c.	No gross reac- tion

*Comment.*—With one exception there was little effect produced by the injection of the transudate collected in the bag around the loop. One dog had immediate vomiting and rapid respiration, followed by several days' diarrhea. Another dog apparently had some slight discomfort which soon disappeared.

**SERIES IV. INCARCERATED OBSTRUCTED LOOP WITH ANASTOMOSIS.**—*Operative Procedures.*—The loop of jejunum was incarcerated and obstructed as in Series III. In addition, a side-to-side anastomosis was performed on the projecting limbs of the loop, re-establishing the continuity of the gut.

TABLE I  
RESULTS IN SERIES I

INJECTED INTO DOG NO.	METHOD OF INJECTION	SOURCE: DOG NO.	MATERIAL INJECTED	TIME AFTER OBSTRUCTION PRODUCED	AMOUNT	RESULT
17	Intra-venous	424	Untreated contents from simple obstruction	72 hr.; natural death	3 c.c.	Violent death
18	Intra-venous	424	Whipple ppt. of contents of simple obstruction	72 hr.; natural death	20 c.c.	No effect
20	Intra-venous	424	Contents from simple obstruction treated by Whipple method	72 hr.; natural death	30 c.c.	No effect
20	Intra-venous	426	Untreated contents of simple obstruction	48 hr.; natural death	15 c.c.	Violent death
21	Intra-venous	426	Whipple ppt. of contents of simple obstruction	48 hr.; natural death	17 c.c.	No effect
23	Intra-venous	423	Purified by Whipple's method from simple obstruction	5 days; etherized	35 c.c.	Slight hyperpnea and nausea

SERIES III, INCARCERATED OBSTRUCTED LOOP.—A loop of jejunum approximately eight inches in length was incarcerated in a thin rubber bag. The afferent and efferent limbs of the loop were then firmly ligated with twilled cotton tape, including in the ligature a portion of the neck of the bag. The ligature on each limb was passed through the mesentery close to the gut, avoiding the inclusion of blood vessels, thus preserving the blood supply of the segment. The omentum was looped about the tie region and held in position with one or two sutures.

TABLE II  
RESULTS IN SERIES II

INJECTED INTO DOG NO.	METHOD OF INJECTION	SOURCE: DOG NO.	MATERIAL INJECTED	TIME AFTER OBSTRUCTION PRODUCED	AMOUNT	RESULT
19	Intra-venous	397 397	Contents of normal intestine		20 c.c.	Vomited vigorously; died during night
34	Intra-venous	373	Contents of normal intestine diluted and strained through gauze		15 c.c.	Shock reaction with hyperpnea, urination and defecation
37	Intra-venous	3 dogs used in Junior Surgery	Normal intestinal contents		20 c.c.	Hyperpnea; and shock; death in 24 hr.
38	Intra-venous	3 dogs used in Junior Surgery	Normal intestinal contents		25 c.c.	Hyperpnea; death in about 5 hr.

## TYPICAL PROTOCOL

Black and brown long-haired mongrel male (weight 12 lb.)

1/3/40 Strangulation

1/4/40 Found dead, 8 A.M.

*Necropsy:* Loop gangrenous but not perforated; intestine above obstruction moderately dilated; below, moderately collapsed; 75 c.c. dark, red fluid which did not clot collected into beaker; characteristic foul odor

TABLE VI  
RESULTS IN SERIES VI

INJECTED INTO DOG NO.	METHOD OF IN- JECTION	SOURCE: DOG NO.	MATERIAL INJECTED	TIME AFTER OBSTRUC- TION PRODUCED	AMOUNT	RESULT
32	Intra- venous	438	Bag contents from obstructed gan- grenous loop	48 hr.; natural death	100 c.c.	Typical violent reaction; died during night; early peritonitis
41	Intra- venous	463	Bag contents from obstructed loop with ligated blood supply	24 hr.; found dead	60 c.c.	Tachycardia
42	Intra- venous	469	Bag contents from obstructed throm- botic loop; gan- grenous and per- forated	48 hr.; found dead	15 c.c.	Shock symp- tom; died dur- ing night
43	Intra- venous	474	Loop contents of obstructed, throm- bosed loop; gan- grenous, not per- forated; early peritonitis	24 hr.; found dead	10 c.c.	Violent reac- tion; died

*Comment.*—Fluid obtained in a bag around a strangulated loop produced marked and severe symptoms when injected intravenously.

**SERIES VII.**—Because of the difficulty of determining by observation of the animal whether any effect is produced by the intravenous injection of intestinal content, another method was sought which could be used independently as a measure of the effect of the injection. This was found in the behavior of the leucocytes. Leucocyte counts were made before injection, five minutes after injection, and twenty-five minutes after injection, and the results are given in Table VII.

## COMMENT

In the eighteen experiments of all types at least two-thirds showed a definite leucopenia induced by the injection. In many cases leucopenia occurred when there was no other apparent effect produced by the injection; but, when objective symptoms were seen, leucopenia always occurred.

In the four experiments of the Series I type (simple obstruction) leucopenia occurred in all, but physical signs appeared in only two.

## TYPICAL PROTOCOL

Brindle bull dog, female (weight 12 lb.)

10/18/39 Obstruction

10/19/39 Dog, which appears well, etherized and posted

*Necropsy:* No gangrene, no peritonitis; anastomosis in good condition and not leaking; loop dilated; 18 c.c. of clear pink fluid which clotted immediately collected from the bag

TABLE IV  
RESULTS IN SERIES IV

INJECTED INTO DOG NO.	METHOD OF INJECTION	SOURCE: DOG NO.	MATERIAL INJECTED	TIME AFTER OBSTRUCTION PRODUCED	AMOUNT	RESULT
25	Intra-venous	428	Bag contents; limbs anastomosed	24 hr.; etherized	18 c.c.	No effect

*Comment.*—Here again no effect was produced by the injection of the fluid obtained in the bag.

SERIES V, MESENTERIC THROMBOSIS.—The mesentery of a large portion of the small intestine was encompassed in a ligature near its vertebral attachment. The ligature was drawn tightly enough to occlude the mesenteric vessels.

## TYPICAL PROTOCOL

Yellow, smooth-haired mongrel female (weight 16 lb.)

12/29/39 Ligation

12/30/39 Etherized and posted

*Necropsy:* Gut gangrenous and serosal vessels injected; 10 c.c. fluid collected from peritoneal cavity and 5 c.c. blood collected from thrombosed vessels

TABLE V  
RESULTS IN SERIES V

INJECTED INTO DOG NO.	METHOD OF INJECTION	SOURCE: DOG NO.	MATERIAL INJECTED	TIME AFTER OBSTRUCTION PRODUCED	AMOUNT	RESULT
39	Intra-venous	459	Peritoneal fluid from mesenteric thrombosis	24 hr.; etherized	10 c.c.	No reaction
40	Intra-venous	459	Blood from thrombosed mesenteric veins	24 hr.; etherized	5 c.c. blood 20 c.c. saline solution	No reaction

*Comment.*—Neither the peritoneal fluid in the abdominal cavity nor blood from the mesenteric veins in a dog with mesenteric thrombosis produced visible symptoms when injected into another dog.

SERIES VI, INCARCERATED STRANGULATED LOOP.—A loop of jejunum approximately eight inches in length was incarcerated in a rubber bag. A ligature of twilled tape was placed firmly about the neck of the bag occluding the lumina of both limbs of the loop as well as the blood supply. The omentum was loosely looped about the ligature and held in place with one or two sutures.

The results obtained in Series VII demonstrate the fallacy of drawing conclusions about the toxicity of material injected intravenously from objective symptoms alone and explains some of the contradictory evidence presented by different investigators. The fact that leucopenia was always produced along with toxic symptoms and was produced also in many animals where no symptoms were manifest indicates that it is a more sensitive index of toxicity.

Using leucopenia as a criterion, our experiments show that the material in a normal intestine and the contents of an obstructed loop both are always toxic when injected intravenously and one is about as toxic as the other.

With the same index of toxicity, the transudate from an obstructed loop is only occasionally toxic, but, if the loop is strangulated, the transudate is always toxic.

Similarly, in the case of the peritoneal fluid in mesenteric thrombosis, although no symptoms occurred when it was injected, definite leucopenia showed that it was toxic.

Although peptones and proteoses are known to produce leucopenia when injected intravenously, the production of leucopenia is not a specific test for them since a number of other substances have the same effect. Leucopenia is, however, in our opinion, an evidence of some type of shock, and the symptoms produced when intestinal content is injected are also a manifestation of some type of shock. The probability is that the leucopenia and the symptoms are both signs of the same phenomenon, but the leucopenia happens to be more constant and more easily detected.

In a consideration of the relationship between the shock, which can be produced by injection of material intravenously, and the symptoms of intestinal obstruction, one factor has always been ignored and that is the factor of time. In order to produce shock, intestinal contents or transudate must be injected within a relatively short period, and in all probability, proteoses, peptones, or other substances which produce shock under the usual experimental conditions could be given very slowly without producing any disturbance in the animal. There is unquestionably something in the bowel which, when rapidly injected, produces shock. This substance or substances pass through the wall of the bowel into the peritoneal cavity when the intestine becomes devitalized, but the intravenous injection of this material can never provide incontrovertible evidence of its role in the causation of symptoms in intestinal obstruction.

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TABLE VII  
LEUCOPENIA INDUCED BY INJECTION

MATERIAL FROM	HOURS AFTER SURGERY	PREPARATION	AMOUNT INJECTED	GROSS SYMPTOMS	FATAL	LEUCOCYTES		
						NORMAL	5 MIN.	25 MIN.
Series I	72	Whipple	30 c.c.	0	0	9000	4400	-----
Series I	48	Filtered through gauze	15 c.c.	++++	+	9500	2200	
Series I	48	Whipple	17 c.c.	0	0	11800	6700	8800
Series I	5 days	Whipple	17 c.c.	++	0	10200	2950	8580
Series II	--	Diluted with H <sub>2</sub> O	15 c.c.	++++	0	16720	1240	6600
Series II	--	Diluted and strained through gauze	20 c.c.	++++	+	17600	12000	
Series III	24	None	20 c.c.	0	0	10200	10800	11600
Series III	48	Oxalated	50 c.c.	0	0	13700	14500	11900
Series III	48	Oxalated	50 c.c.	0	0	9600	2000	
Series III	72	Oxalated	15 c.c.	0	0	14400	12100	15860
Series III	72	Oxalated	40 c.c.	0	0	16000	14000	14150
Series III	96	Oxalated	50 c.c.	0	0	14660	12000	14000
Series V	24	Diluted and strained through gauze	25 c.c.	++	+	15000	10000	8000
Series V	24	None	10 c.c.	0	0	14920	11500	10200
Series V	24	None (blood)	5 c.c.	0	0	6880	5100	6200
Series VI	24	None	60 c.c.	+	0	11000	2200	14500
Series VI	48	None	15 c.c.	++++	+	11800	3000	-----
Series VI	24	None	10 c.c.	++++	+	14400	5400	

In the two experiments where normal intestinal content (Series II) was used, symptoms and leucopenia were present in both.

There were no objective symptoms in the six experiments in Series III (transudate in bag around obstructed loop). In one there was a striking leucopenia and in two there was a very slight reduction in the white cells.

In the cases of mesenteric thrombosis (Series V) the fluid in the abdominal cavity produced symptoms in one instance but not in the other, but there was a leucopenia in both. Blood from the mesenteric veins from one of the mesenteric thrombosis dogs produced no symptoms and no leucopenia.

Fluid from a bag around an obstructed strangulated loop (Series VI) produced symptoms and leucopenia in all instances.

#### DISCUSSION AND CONCLUSIONS

We are unable from this study to draw conclusions about whether or not a bag around an obstructed loop prolongs the life of the experimental animal for two reasons: (1) The bag filled up so rapidly with fluid that if the dog were not sacrificed, the bag would become over-distended and leak. (2) Even though the obstructed loop was in a bag, the animal still had an intestinal obstruction above the loop.

## INTUSSUSCEPTION IN AN ADULT DUE TO SUBMUCOUS LIPOMA OF THE ILEUM

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**I**NTUSSUSCEPTION in adults is a rare but important cause of intestinal obstruction. It is well known to students of the condition that a definite cause for intussusception, usually tumor, is commonly found when it occurs in adults; whereas, in cases occurring during infancy, a causal factor is rarely found. In this report we wish to present and to comment upon a case of intussusception in an adult due to a submucous lipoma of the ileum.

### CASE REPORT

C. M., a white single male, aged 57 years, entered the hospital July 24, 1940, complaining of generalized abdominal pain of forty eight hours' duration. The pain was sudden in onset and was colicky. There was no radiation of the pain and the patient stated that it was localized in the region of the umbilicus. There had been no previous attacks of abdominal pain. About twelve hours before entry the pain became more severe but was of the same character. Shortly after the onset the patient began to vomit everything taken by mouth and continued to do so. The bowels did not move after the pain began, but previously there had been no changes in the bowel habits. No bloody or tarry stools had ever been noticed. The patient's health in the past had always been good except for a perianal abscess five years before.

One brother had carcinoma of the rectum. There was no family history of diabetes, tuberculosis, or diseases of the blood.

On examination the patient was a well developed, moderately obese, middle aged man who appeared acutely ill. The heart and lungs were normal. The abdomen was distended and there was tenderness in the right lower quadrant. No masses were palpable and no peristalsis was audible. Rectal examination showed a symmetrically enlarged prostate, and there was bloody mucoid material on the examining finger. The rectal temperature was 99°, the pulse was 120, and the blood pressure was 170 systolic, 100 diastolic. Admission diagnosis was acute intestinal obstruction. Examination of the blood showed a red cell count of 4,600,000 with 90 per cent hemoglobin (Tallqvist) and a white cell count of 9,400 with 89 per cent polymorphonuclear leucocytes, 9 per cent lymphocytes, and 2 per cent monocytes. The urine was normal except for a rare white blood cell. The Wassermann test was negative.

Parenteral fluids were administered to the patient, and shortly after entry he passed a bloody, watery stool. A barium enema was given soon after entry. The report was as follows: "The opaque enema filled the colon rapidly and well up to the ileocecal region, where there was a central filling defect 5 cm in width and 8 cm in length. This was apparently entirely inside the cecum and ascending colon with no defect in the wall of the bowel, but there was a concavity in the ileocecal valve. The film after evacuation shows valvulae conniventes of small

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various intervals strands of dense connective tissue extended among the fat cells of the tumor. In a few regions there was foreign body reaction to fat liberated by the breakdown of tumor cells. Except for some hemorrhage in the mucosa and edema in the submucosa, the other tissues of the intestinal wall were not altered from the normal."

#### COMMENT

This was the fifth instance of intussusception in adults at the Peter Bent Brigham Hospital between the years 1913 and 1940. In only one case was no exciting cause found. The causes in the remaining cases were: lymphoma of the ileum, congenital band of the ileum, and submucous lipoma of the ileum. The case presented above is the second intestinal lipoma causing intussusception at this clinic. The previous instance of lipoma of the ileum caused recurring intussusception and

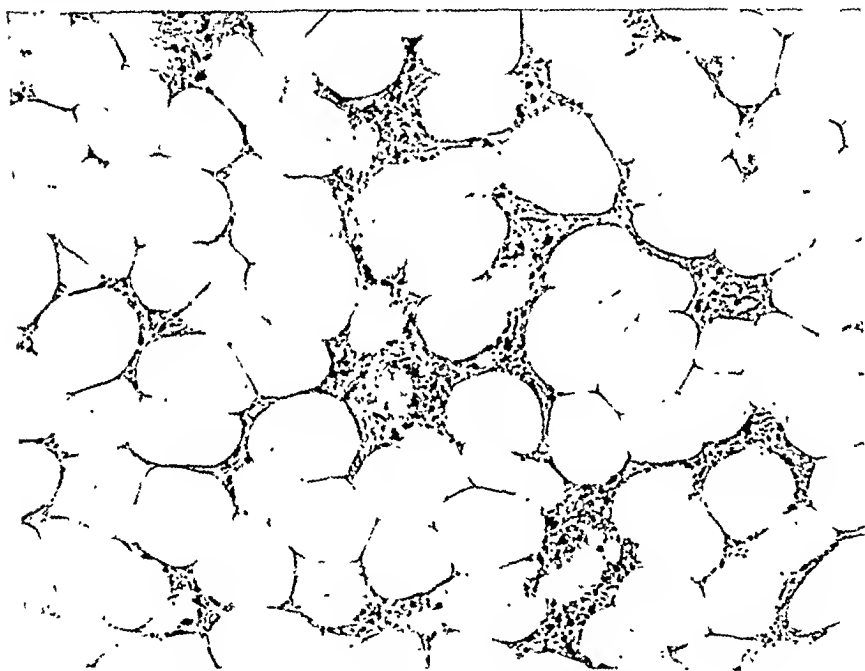


Fig. 2—Photomicrograph of a section of the submucous lipoma of the ileum.

has been reported by Oughterson and Cheever.<sup>1</sup> The finding of an etiological agent in four out of five patients agrees with the experience of most surgeons with intussusception in adults. This is in striking contrast to the problem in infancy and childhood as is well illustrated by the study of 372 cases of intussusception in those age groups by Ladd and Gross<sup>2</sup> in which a causal factor was discovered in only 5 per cent of the series.

Poston,<sup>3</sup> in 1934, pointed out that intestinal lipomas are uncommon and collected 80 cases from the literature in which intussusception was initiated by a lipoma of the intestinal tract. We have found 15<sup>4-16</sup>

bowel inside the large bowel. This is conclusive proof of intussusception of the small bowel into the cecum and ascending colon."

With a preoperative diagnosis of intussusception operation was undertaken about five hours after admission. Under ether anesthesia a right paramedian incision was made; when the peritoneal cavity was entered, the leading point of an ileoileal intussusception was found approximately 15 cm. proximal to the ileocecal valve. The mass was about 20 cm. in length and was easily reduced. The blood supply was in excellent condition but there was considerable edema present. When the intussusception was reduced, the leading point was found to coincide with a pedunculated mass the size of a walnut within the lumen of the bowel. There was dimpling of the antimesenteric border of the ileum where the mass was attached. Resection of the portion of the intestine containing the tumor was performed and the continuity of the lumen was restored by an end-to-end anastomosis. The wound was closed and the patient returned to the ward in good condition.



Fig. 1—Photograph of the specimen opened, showing the pedunculated lipoma and hemorrhage and edema of the mucosa of the ileum

The patient was febrile for four days postoperatively and on the seventh and eighth postoperative days. The cause of the fever was a recurrence of an old perianal abscess. This was incised and drained and the fever promptly subsided. The abdominal wound healed *per primum*. The patient was discharged on the sixteenth day after operation, at which time he was asymptomatic and eating a full, house diet.

The pathologist's report of the specimen (Figs 1 and 2) was benign submucous pedunculated lipoma of the ileum. "The tumor was composed of fat cells of adult type. There were no areas of fetal fat tissue or of spindle cells. At

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additional cases of the same nature reported since 1934. It is not difficult to visualize the mechanics of intussusception initiated by a pedunculated intraluminal intestinal tumor, such as a lipoma. According to Wardill,<sup>17</sup> the tumor acts as a foreign body within the lumen of the gut and produces spasmodic contraction of the gut around it and inhibition of the bowel just distal to it. Thus, the bowel is prepared to invaginate, and the contracted portion with the tumor may enter the dilated segment.

The clinical picture of intussusception in adults is usually not as clear cut as that in infants. However, the present case presented colic-like abdominal pain, nausea, vomiting, obstipation, and grossly bloody stool. No mass was palpable but otherwise this instance from a clinical viewpoint was very similar to intussusception in infants. More often intussusception in adults is less acute and the symptoms are milder and recur at varying intervals. Grossly bloody stools are seldom seen, and a mass in the abdomen is not commonly palpable. The barium enema will make the diagnosis if the intussusception is of the ileocolic type, as it did in this case. However, if the advancing point of the invagination has not entered the ileocecal valve, the disease cannot be ruled out by barium enema. Moreover, if the symptoms are at all suggestive of intestinal obstruction, it is not desirable to give barium by mouth.

The catholie method of treating intussusception is operative. The invaginated bowel is reduced and a thorough search for tumor should be made. If tumor is found, as it is in the majority of cases in adults, it should be removed. *It must be remembered that the benign tumors of the bowel such as lipoma, adenoma, and polypi may be multiple.* As pointed out by others,<sup>1</sup> if a tumor is not found at the apex of the intussusception, the bowel should be examined both proximally and distally, since the tumor is not always the exact leading point of the intussusception. The therapeutic use of the barium enema in intussusception has been advocated by a few for many years and more recently by Williams.<sup>18</sup> The disadvantages of this use of the barium enema seem to us far to outweigh the advantages.

#### SUMMARY

1. A case of intussusception in an adult due to a submucous lipoma of the ileum is reported.
2. Ninety-five cases of intussusception in adults due to lipomas of the intestine are found in the literature.
3. The value of the barium enema in making the diagnosis is pointed out and its limitations noted.
4. Intussusception in adults is frequently initiated by intestinal tumors and the importance of searching for tumor in adults at operation for intussusception is stressed.

undigested food, blood in the intestines, ulcers either primary or secondary to foreign bodies, and circulatory disturbances of the mesenteric vessels. A local enterospasm incident to or following either the spontaneous or operative reduction of a strangulated hernia may be sufficient in degree to produce an intestinal obstruction. This type of mechanism, local in its stimulation, is easy to understand and may be accepted almost without reservation. On the other hand, the cases in the second group, in which the causes of a reflex ileus have been ascribed to distant foci are less clear. Some have been ascribed to lesions involving the celiac plexus. Others seem to follow contusions of the abdomen, and many which appear incident to operative trauma have been grouped under "postoperative spastic ileus." Then there are some cases which seem to accompany lesions of other organs, either intra- or extraperitoneal in their location. The third and final group, embracing causes which act by way of the central nervous system, include both those cases in which the lesions are organic in nature and those which have been ascribed to psychogenic disturbances.

The pathologic appearance of obstructing lesions in the large bowel at the time of operation is extremely varied. Either one or more of its major anatomical partitions or the entire colon from the cecum to the rectosigmoid may be so firmly contracted that the bowel is almost ropelike in appearance and consistency. Usually, however, the area involved is much smaller in its extent and may involve but a few inches of the bowel. This area is ordinarily represented by a firm, hard, smooth mass which seems almost bloodless and appears anemic. At other times the area is definitely constricted and the bowel appears as though it were tied with a cord. If the spasm has been present for a long period of time, not only the colon, which is proximal to the obstruction, but the entire small intestine may be dilated and atonic. While these findings may be present at the time of operation, they may disappear under the manipulations of the surgeon. It should also be borne in mind that an obstruction which may have been demonstrated both clinically and by x-ray may disappear completely under the influence of anesthesia. In these cases the operator may find nothing to account for the intestinal obstruction. In rare instances the evidences of muscular spasm have been known to persist even after death, although the lesion at this time is usually recognized only by the dilatation of the bowel above the point of the original spasm. Histologic examination of this area as a rule reveals nothing, although in one case, which will be subsequently mentioned, there was hypertrophy of the intestinal musculature. Occasionally a spastic intestinal obstruction may follow a surgical operation. This may be verified either at the time of the second exploration or at autopsy.

It might be instructive at this point to review some of the reported cases and those in our own series, classifying them according to the location and the extent of the colonic spasm.



## COLONIC SPASM AS THE CAUSE OF INTESTINAL OBSTRUCTION

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THE finding of either a spastic cecum or sigmoid flexure in the course of a routine physical examination is a frequent observation and occasions very little comment. However, a muscular spasm of the large bowel which is sufficient in its intensity and duration to occlude fully its lumen and thus produce an intestinal obstruction is rare. In 1896 Murphy,<sup>13</sup> while operating upon a patient suffering from lead poisoning, found a spastic obstruction in the bowel. A year later Heidenhain<sup>5</sup> presented 3 cases of spastic ileus before the German Surgical Congress. While the interpretations of his observations were seriously doubted at the time, subsequent case reports have given unqualified support to his original contentions. Nagel,<sup>14</sup> in 1910 was able to gather 51 cases from the literature and reported 2 of his own in which spasm of the wall of either the small or large intestine was so marked that an intestinal obstruction occurred. Zimmerman<sup>27</sup> in 1930 in a collective review of this interesting subject reported 150 cases in which the condition had been definitely demonstrated either at the operating table or at post-mortem examination or both. To this number he added 2 observations of his own. Steigmann and Singer<sup>26</sup> reported 15 cases, including 1 of their own, in which an idiopathic neurogenic spastic ileus terminated fatally. Our interest in this subject was stimulated by the recent observation of 5 cases of large bowel obstruction in which a preoperative diagnosis of malignancy was made, and in which subsequent events warranted the diagnosis of muscular spasm as the cause of the obstruction. Perhaps a review of these cases and some similar ones reported in the literature might prove instructive and again emphasize the importance of a muscular spasm as a definitive cause of large bowel obstruction.

The etiology of spastic ileus which may similarly affect not only the large but the small intestine as well is indeed obscure. While many different theories have been advanced, none adequately explain the underlying mechanism. Zimmerman<sup>27</sup> stated that the causes may be divided into three main groups, corresponding to the three major divisions of the nerve supply to the bowel. These are essentially: (1) a spastic ileus due to stimuli acting on the bowel at the site of the local spasm; (2) a reflex spastic ileus secondary to distant lesions; and (3) an ileus secondary to causes acting by way of the central nervous system. The first variety characterized by local muscular contractions may be due to foreign bodies, such as scybala, gallstones, intestinal parasites,

noted only in the ascending and descending portions of the colon. During the day the patient had only one vomiting spell, producing very little material. There was no meteorism. A day later the spasm of the intestine had cleared up. Within the next ten days the spasm was again manifested by very firm contraction of the ascending colon and later also the transverse colon. About thirty-six hours later violent stercoraceous vomiting was noted and recurred a day later in the presence of an intensely contracted transverse colon. No contraction was found in the rectum on digital examination. The patient did not complain of abdominal pain. Progressive improvement followed another attack of stercoraceous vomiting four days later and the patient was discharged after several weeks.

The case of von Leube<sup>5</sup> is particularly interesting because the patient, while under observation, presented a complete outline of the spastically contracted colon at one time, while at subsequent examinations only certain areas of the colon seemed to be involved.

In two cases in which an extensive involvement was recorded Bunge<sup>3</sup> states that an area in the transverse colon was dilated while the colon proximal and distal to this was definitely contracted.

Bunge,<sup>3</sup> Case 1: A highly neurotic female was subjected to a gynecologic operation combined with appendectomy. For several days after the operation the patient complained of severe pain of colicky character in the upper part of the abdomen. There were no objective symptoms; the abdomen was soft and not tender. Purgatives and high enemas, and finally atropine subcutaneously, failed to relieve the fecal retention on the third day after operation. The meteorism attained an alarming degree on the fifth day. The stomach contained 2 liters of feculent material. The introduction of a rectal tube was impossible because of a spastic contraction at Houston's valve. Laparotomy showed extreme distention of small intestine and cecum, the latter passing abruptly to the colon ascendens which was contracted to the width of a thumb. All segments of the colon including the sigmoid flexure were contracted like a taut rope. An ileostomy was performed. On the second day stools passed by rectal route. The patient made a recovery.

Bunge,<sup>3</sup> Case 2: A female had a gynecologic operation combined with an appendectomy. There were no subjective postoperative pains but she developed the signs of an intestinal paralysis. Various therapeutic measures resulted in the passing of some flatus on the second and third days, and some inspissated feces on the fourth day. Meteorism, however, increased and aspiration of the stomach yielded feculent fluid. The pulse was 108 and of poor quality. A laparotomy showed that the small intestines were greatly distended, although not to the degree as in Case 1. The cecum was empty and contracted but not as much as the colon ascendens, which was in a state of maximum spasm and was as hard and stiff as a rope. The same appearance was presented by the transverse colon with the exception that its mid-portion was distended to a fist size by gas. The colon descendens and the sigmoid were in the same state as the colon ascendens. An ileostomy was performed. However, the patient died seven days after operation. Autopsy revealed the absence of any signs of peritonitis; the intestine, which had been contracted at operation, was greatly dilated and filled with gas as far as the rectum. Bunge holds that the most plausible etiology in both cases may be seen in nervous reflex mechanisms.

The more common variety of cases, however, are those in which the muscular contraction appears to be definitely localized to a small area of the colon. No area of the bowel appears immune. In one of the present series the area just distal to the cecum was spastic.

The entire colon from the cecum to the rectosigmoid may be spastically contracted as was noted in the case of Pons Tortella and associates.<sup>19</sup>

Pons Tortella, Ferrándiz Senante, and Subirana:<sup>19</sup> A male, aged 53 years, was admitted with a history of five days of obstipation accompanied by recurring violent abdominal pain. From the onset the patient took only liquids which he promptly vomited. There was a history of gastroenterostomy performed thirteen years previously. Physical examination disclosed a well-developed male. The abdomen was distended. The peristalsis was visible when induced by external stimulation. The condition grew worse on the day of admission and spontaneous vomiting of nonfeculent character occurred. A diagnosis of mechanical occlusion caused by adhesions was made. Laparotomy, with spinal anesthesia, revealed a large intestine intensely contracted between cecum and sigmoid, so as to resemble a rope of a finger's thickness. No adhesions or bands were found. The operative diagnosis was an intestinal obstruction caused by spasm of the colon. Antispasmodics were given for the first few days postoperatively and the course was uneventful.

It is more usual, however, for a spasm of this extent to begin distal to the cecum.

Nordmann:<sup>16</sup> A female, aged 45 years, gave a previous nine-year history of mild colicky pain in the right upper quadrant, which for the past two years had become less severe. Twelve hours prior to admission there was a sudden intense attack of abdominal pain associated with vomiting. Marked constipation was noted. Patient appeared moderately strong and healthy. Pulse: 76, regular. Temperature was normal. The vomitus consisted of a feculent fluid, biliary in color. There was no corneal reflex. The pharyngeal reflex was present and patellar reflexes were active. There was a marked general hyposensitivity. Deep pinpricks were not felt in the left leg and right arm. There were no other neurological symptoms. The abdomen was slightly distended. There was pronounced tenderness below the umbilicus. A diagnosis of peritonitis was made. Operation disclosed nothing abnormal with the exception of a distended cecum which led to a severely contracted colon, which extended to the pelvic sigmoid. The walls felt hard and rigid. On gentle pressing of the cecum some gas entered the contracted segment. For ten days following operation, there was fecal vomiting, which ceased on the eleventh day. Convalescence was uneventful.

Marquardt:<sup>10</sup> A patient, aged 17 years, was seen in the fifth month of pregnancy. Operation was performed for a severe suppuration of the kidney pelvis. Three days later after a severe diarrhea the patient complained of an intense pain in the region of the appendix and coincidentally developed a paralytic ileus. Seventy-two hours later, when all therapeutic measures had failed, an exploration was performed. No organic obstruction was found, but the cecum was extremely distended while the entire colon as far as the rectum was contracted. A cecostomy was performed. The patient died. At autopsy no obstruction was discovered and the lumen of the colon appeared normal. There was no peritonitis.

Von Leube:<sup>8</sup> A female, aged 19 years, had been suffering from "vomitus nervosus." The stomach emptied within normal time limits and there was no reduction in gastric acidity. Suddenly, in the absence of any unfavorable change in her general condition, she vomited greenish gray material of marked feculent odor. Physical examination revealed that several tumorlike resistances were palpable in the right hypochondrium. A rectal tube was introduced 60 cm. into the anus without result. The following day a ropelike contraction, approximately the size of a little finger, was palpable along the entire course of the large intestine from cecum to sigmoid flexure. The observation could not have been more definite if an anatomical specimen were available. In the evening of the same day contraction was

perforation was noted near the hepatic flexure. In the midportion of the transverse colon a constricting ring obliterating the lumen of the bowel was evident. Distal to the contraction area, the large intestine was found empty and collapsed. Application of warm saline solution failed to relieve the contraction. Death supervened six hours after operation. The autopsy findings are the same as the findings at operation. The ureter presented spastic contraction.

Rummert:<sup>21</sup> A male, aged 76 years, came to the clinic complaining of severe spastic abdominal pain of great severity which had recently been complicated by vomiting. Six months previously he changed from the customary mixed diet to a raw diet. Obstinate constipation followed and the patient suffered from abdominal pain. In the past weeks these pains became more intense. Oatmeal gruel brought some relief. Examination revealed a myocardial lesion. A taut, ropelike body as thick as a finger and tender to pressure was palpable along the course of the transverse colon. The ileocecal region was distended. X ray examination revealed normal contours of the stomach. The small intestine was filled at the end of eight hours and presented fluid levels with considerable gas distention. At the end of twenty four hours, the colon was filled as far as the sigmoid and exhibited marked spastic haustration. There were no other pathologic findings. A diet, bellafolin, and warm applications over the abdomen produced bowel movements and improvement.

Melehuor<sup>11</sup> felt that the chronic torsion of the omentum observed in his patient may have caused a disturbance of the innervation which manifested itself in the spasm of the transverse colon, although he admitted that a purely mechanical compression of the colon by the twisted omentum could not be ruled out. Steindl<sup>25</sup> brings forth a few points of interest in regard to his case. Histologic examination of the colon gave no evidence of pathologic changes. He, too, felt that the spasm in this particular area might have been due to an expression of a functional disturbance due to disorders of the higher centers in the vegetative system. It is interesting to note that in this case the spasm was localized to the border area between two systems of innervations. Many observers have stated that muscular contractions occasionally occur in such border zones. Evidently in these cases there may have been a disturbance in coordination between the central nervous and sympathetic systems.

There were four cases in which spasm of the splenic flexure was sufficient to cause an obstruction. To this group I wish to add two additional cases of my own, Cases 2 and 3.

Schmid:<sup>22</sup> A female, aged 30 years, had suffered for four weeks from a "burning sensation" in the abdomen, accompanied by colicky pains on the right side, associated with vomiting. There was a constant thirst and the patient was very nervous. Bowel movements were eluted only with enema, and the stools were sometimes black, and at other times covered with a fibrous membrane. Three physicians were consulted, one diagnosed the condition an "inflammation of ovaries," another spoke of it as a "nervous ailment," and the third regarded it as "90 per cent nerves." Upon admission the patient appeared pale. The pulse was 120. The heart and lungs were negative. The abdomen was not prominent but slightly tender. There was an undefinable resistance across the whole of the lower abdomen. The condition was considered to be one of tubercular peritonitis.

The patient was observed for a period of three days, during which time there was nausea, but no vomiting. The bowels moved with difficulty. X rays revealed

CASE 1.—\*(No. 430897.) B. H., a housewife, aged 48 years, was admitted to the private service on Oct. 14, 1938, and discharged on Nov. 15, 1938. This patient had had a cascade type of stomach and recently had complained of attacks of pain in the right lower quadrant accompanied by a feeling of fullness and abdominal distention. During these episodes she experienced several attacks of loose stools. Physical examination revealed some abdominal distention but no masses were palpable and rectal examination was negative. The stools failed to disclose the presence of occult blood. Barium enema on several occasions revealed a constricting lesion of the proximal ascending colon, just distal to the cecum, which was thought by some to be malignant in nature. Accordingly, on Oct. 19, 1938, under ethylene anesthesia, a lower left rectus muscle-splitting incision was made. There were several bands running from the parietal peritoneum to the mesentery, apparently constricting the cecum and lower ascending colon. The appendix was long, and its indurated tip was buried subserosally and retroceally. The adhesions were divided and appendectomy performed. The abdomen was closed in layers, using chromic throughout and pincettes for the skin. Following operation the patient became terrifically distended. A Levin tube gave slight relief. Small amounts of gas were passed by rectum. On the sixth day after operation patient had a rise in temperature to 104°, distention increased, and x-ray revealed a high right diaphragm suggestive of a pneumonic process of the right base and a distended loop of small intestine with fluid levels. Although x-ray seemed to indicate definite intestinal obstruction, repeated rectal irrigations yielded gas and small bowel content. The temperature gradually fell to normal and the abdominal distention became less. On the tenth day a wound dehiscence was noticed with prolapse of omentum. This was replaced into the peritoneal cavity and the wound packed. The patient was discharged on the twenty-seventh day with a granulating wound. Subsequent x-rays revealed a spastic constriction of the ascending colon, yet slightly less in degree. The patient was readmitted on May 3, 1939, for repair of a ventral hernia. This operation was uneventful. She has been seen subsequently and has no complaints. The adhesions about the ascending colon were not sufficient to account for the constriction present in the x-ray, and even though these were divided, the postoperative x-ray film still showed that the constriction was present. It must be assumed that the obstruction was caused by a localized muscular spasm.

Melchior:<sup>11</sup> A male, aged 31 years, gave a history of recurrent pain in the upper part of the abdomen and occasional feeling of tension above the umbilicus. Three months prior to entrance, an x-ray examination by another physician showed a spastically contracted transverse colon. Twenty-four hours before admission, a drawing pain was felt, especially in the right part of the abdomen. There was no bowel movement. A preoperative diagnosis of appendicitis was made. At operation, the omentum which was partly necrotic and partly infarcted, was twisted three or four times about its axis; the spiral touching the transverse colon appeared stenosed. Following excision of the omentum, the patient made an uneventful recovery.

Steindl:<sup>25</sup> A male infant was seen sixty hours after a normal birth. The midwife stated that there had been no bowel movement since birth. The vomiting began on the day before admission and was gastric at first and subsequently became feculent. The child was well developed, the pulse regular, and the respirations shallow. The temperature was 36.4° C. The abdomen was distended and tympanitic throughout. Gentle palpation elicited obvious signs of pain. A diagnosis of ileus, and possibly peritonitis, was made. At operation the small intestine was greatly distended and mesoconium was found between the loops. The ileum was turned almost 360° about the mesenteric root. Detorsion was done. The cecum and descending colon were immensely distended and filled with meconium and a

\*The numbered case reports are those of my own patients.

during the first two days at the hospital. The abdomen was distended with meteorism. Violent vomiting set in on the third day and stools continued to pass regularly. X-ray examination before barium meal showed several fluid levels and extremely distended bowels, probably in both small and large intestines. There was normal emptying of contrast meal from the stomach and small intestine. Contrast meal was visible in the ascending colon at the end of fifteen hours. There was no progress at the end of twenty-three hours. Contrast enema revealed abrupt stoppage in the middle of the transverse colon. A diagnosis was made of spastic obstruction of passage in the transverse colon. The condition of the infant grew steadily worse and vomiting continued. Conservative treatment was ineffectual. The infant died on the eighth day after admission with signs of pneumonia. Autopsy showed the small intestine and colon were greatly distended as far as the splenic flexure. From the flexure through the other segments the lumen of the large intestine was narrowed. There was no organic obstruction. There was probably a spastic obstruction of the passage.

CASE 2.—(No. 386417.) F. K., a female, aged 70 years, was admitted as a private patient on Nov. 5, 1935, and discharged Nov. 21, 1935. Fifteen years before, the patient had had an ovarian cyst removed. Six weeks prior to admission she had been experiencing pains in the left loin and left upper abdomen. She noticed that she was constipated and was slightly constipated. She had lost seven pounds in weight. Urinalysis and flat plate of the abdomen were negative. A gastrointestinal series disclosed a constricting lesion in the region of the splenic flexure which a barium enema verified and which did not disappear after atropinization. The stools were guaiac negative. Physical examination disclosed an elderly female with evidence of arteriosclerosis. The abdomen was slightly distended but not tender. Under spinal anesthesia and through a left paracostal incision the abdomen was explored, but no pathology was found in the colon. Following operation the patient developed a bronchopneumonia which cleared up very slowly. The wound healed by primary union. About a month after discharge she developed a lobar pneumonia and died.

CASE 3.—(No. 436200.) M. K., aged 81 years, was admitted to the hospital for the first time on Feb. 13, 1939, and discharged Apr. 17, 1939. He entered complaining of lower abdominal cramps and obstipation of three days' duration. Patient had had an easily reducible right hernia for twenty years which had given him no recent trouble. Three days before admission he began to have diffuse lower abdominal cramps during which time there was no passage of feces or flatus despite enemas. There has been no nausea or vomiting. Temperature at home according to the patient was 101°. There has been no melena, rectal bleeding or mucus, but in the preceding months the patient had complained of increasing constipation. Examination revealed a well-developed, fairly well nourished old man who did not appear acutely ill. Temperature was normal. Chest was emphysematous. Heart was enlarged to the left, and the sounds were of good quality. The abdomen was flat and soft. There were no masses and no spasticity. A distended cecum could be felt in the right lower quadrant. Rectal examination revealed bilateral tenderness and there was no visible peristalsis. Blood pressure was 170/96. Hemoglobin was 75 per cent, white blood count 14,000 with 75 per cent polymorphonuclears. X-ray examination of the abdomen showed a large amount of gas in the right half of the colon proximal to the descenders. There was no definite indication of gas below this. There was moderate dilatation of the small bowel. Barium enema examination showed an obstruction to the passage of barium in the region of the splenic flexure. The actual lesion was not demonstrated because barium could not be injected beyond this site.

On Feb. 13, 1939, under local anesthesia and through a McBurney incision, the cecum presented into the wound and was very much dilated. The cecum was

a rapid emptying of the stomach with filling of the small intestine. The large intestine did not fill. Exploration was decided upon but the patient died rather suddenly.

The autopsy revealed a firm constriction in the proximal portion of the splenic flexure with hard scybala distal to it. The barium, however, had not proceeded beyond the ileum. Examination of the constricted area failed to reveal either a tumor or ulceration. There was no compression visible from the outside, nor was there evidence of peritonitis.

Henle:<sup>6</sup> A male, aged 64 years, was referred to the hospital with a diagnosis of ileus and a functional weakness of the heart. Two weeks previously he had fallen upon the left side of his chest. For the past two days he had had generalized abdominal cramps, and during this period he had suffered from obstipation. Physical examination revealed some evidence of myocarditis. The abdomen was distended but not tender. A diagnosis of pancreatic disease with paralytic ileus was made. Operation disclosed no evidence of either pancreatic disease or peritonitis. The transverse colon was greatly distended. There was a definite constriction in the region of the splenic flexure. The constriction gradually disappeared after manipulation. On the assumption that the condition was one of spastic ileus, the wound was closed. The patient died the following day of cardiac decompensation. Autopsy showed an arteriosclerosis, moderate in descending thoracic and abdominal aortae, but marked in the left coronary artery. There was a brown atrophy of the heart. Emboli were present in both main branches of pulmonary arteries. There was a hemorrhagic infarct in the left lower lobe and numerous thrombi in the prostatic plexus. A paralytic ileus of all intestines with loose agglutination of coils of small intestine was noted.

Brink:<sup>2</sup> A male, aged 25 years, well developed, and with no previous history of gastric trouble, suddenly took ill with acute abdominal pain referred to the left hypochondriac region, and a "feeling of fullness" in the abdomen. The pains in the abdomen were colicky in character and were accompanied by severe cramps in the calves of the legs and anterior thigh muscles, causing him to scream with pain. Morphia injections had no effect on the pain, but atropine eased the attacks. Patient was seen twelve hours after the pain started. He had attacks of nausea and vomiting, and enemas were ineffectual. The patient was taken to the hospital and here an enema gave a slightly colored result but without relief of the pain. The physical examination was negative; only slight tenderness and resistance to deep pressure over the transverse colon was found. The patient's general condition, pulse and temperature, remained good. He was put on 1/100 to 1/50 gr. atropine injections daily as required for the pain, and he was given bromides for his insomnia and anxiety. Further examination of the nervous system, gastric lavage, and stools proved negative. Twelve hours later there was a copious bowel movement which contained no pathologic elements. After this attacks of moderate severe colic recurred, but these were kept in abeyance with 1/150 gr. atropine hypodermically. Three days later when a contrast enema was given, it was found that the barium passed in freely two inches beyond the splenic flexure where it remained for fifteen minutes without progressing further. After this period it was decided to take a film of this spasm. The patient was turned on his abdomen and a film taken. On the film the spasm was still visible but a thin trickle of barium was seen to be passing further into the transverse colon. The further progress of the patient was uneventful and when last heard of, after eighteen months, he had had no further attacks.

Liehti:<sup>9</sup> A female infant was admitted fourteen days after a normal birth. Four days before admission to the clinic the infant began to suffer from vomiting independent of meals. When first seen the child did not seem to be seriously ill. The infant fed well and bowel movements were regular. There was no vomiting

involved simultaneously. Spasm in this location is not a rare preoperative finding nor an unusual postoperative complication. It is, as a rule, transient and of little significance. However, it may be the cause of the obstructive symptoms, as is attested by the cases reported by Korte,<sup>7</sup> Guillaume,<sup>4</sup> Licht,<sup>9</sup> Schaeffer,<sup>22</sup> Sohn,<sup>24</sup> and Cases 4 and 5 of my own present series.

Korte,<sup>7</sup> Case A. A male, aged 68 years, was admitted to the hospital with an intestinal obstruction of three days' duration. A laparotomy showed intense contraction of the descending colon and sigmoid flexure. A cecostomy was performed. Death occurred on the following day and autopsy showed "parenchymatous nephritis, spasm of sigmoid." No tumor or other cause for the obstruction was found.

Korte,<sup>7</sup> Case B. A female, aged 69 years, was taken ill on Nov. 28, 1912, with all the symptoms of intestinal obstruction manifested by feculent vomiting and ineffectual enemas. A diagnosis of intestinal obstruction was made. A laparotomy performed on Nov. 30 showed an "enterospasm in the lower portion of the small intestine, descending colon and sigmoid flexure, but no mechanical obstruction." The bowel was sponged with saline solution. An evacuation followed four days later after the administration of castor oil. She was discharged well on the twenty-fifth day.

Korte,<sup>7</sup> Case C. A female, aged 75 years, was admitted with an intestinal obstruction of four days' duration. A diagnosis of a tumor or strangulation of the bowel was made. The cecum was found to be greatly distended and a cecostomy was provided. The first evacuation through artificial anus occurred seven days after operation. Since there were no bowel movements by the natural route, a tentative diagnosis of stenosing carcinoma of the intestine was made, and a second laparotomy was performed eight months later. No tumor or other obstruction was found, but the colon, especially in the sigmoid flexure, was contracted and had a ropelike appearance. A cecosigmoidostomy was performed and eleven days later an ileostomy. Death occurred eight days after the last operation. Autopsy revealed no evidence of peritonitis and no obstruction of the intestine. There was no history of abnormal nervous phenomena.

Korte,<sup>7</sup> Case D. A female, with a previous history of ulcerative colitis with recovery in 1907, was admitted in 1921 for increasing constipation, severe intestinal colic, and perceptible intestinal contraction. A tentative diagnosis of intestinal obstruction due either to adhesions or cicatricial stricture was made. Laparotomy showed that the colon as far as the sigmoid flexure was tightly packed with hard fecal masses and that the pelvic colon was intensely contracted. There were no other abnormal findings. A left-sided colostomy was performed. Four months later the intestinal function was normal. The condition was unchanged in 1923.

Korte,<sup>7</sup> Case E. A male, aged 56 years, gave a history of periodic attacks of intestinal colic for the past four or five months. There was meteorism. A ropelike formation was palpable in the region of the sigmoid flexure. A laparotomy showed a spasm of the small intestine and intensely contracted, ropelike sigmoid flexure. Recovery took place.

Guillaume.<sup>4</sup> A male, aged 40 years, was first seen five days after a sudden onset of colic marked by constipation. From then on he gradually lost appetite, was nauseous, but did not vomit. A ray examination without barium meal showed no gaseous distention. Believing that this condition was due to a spastic state of the intestine, the author prescribed belladonna. The colics were mitigated, but the condition remained unchanged. Another roentgenogram taken two days later



extraperitonealized and fixed by interrupted sutures to the peritoneum. Iodoform packing was placed about the suture line and a few fascial and skin sutures were taken.

On Feb. 14 the cecum was incised without the escape of gas or stool. Temperature was 102°; pulse, 30. On Feb. 15 the cecostomy was irrigated with the discharge of gas and stool. On Feb. 16 temperature was lower and the cecum was discharging spontaneously. On Feb. 18 packings were removed. On Feb. 23 barium enema x-ray examination made on two separate occasions failed to show any evidence of an organic lesion in the colon. The region of the splenic flexure was particularly studied. On Feb. 24 patient had been passing flatus and stool from the rectum for several days. On Feb. 28 the cecum was closed extraperitoneally under local anesthesia. Following this the patient made an uneventful recovery and was discharged March 17, 1939. He was last seen in March, 1940. His general condition was good and his bowels moved once a day. He had an incisional hernia.

Of the six cases in which spasm of the splenic flexure was the cause of the ileus, one presented by Schmid<sup>23</sup> was thought to have been an ileus on the basis of chronic peritonitis. Autopsy showed a constriction in the proximal portion of the splenic flexure. A case reported by Henle<sup>6</sup> was diagnosed as acute pancreatic disease accompanied by paralytic ileus. At operation a definite contraction was found at the splenic flexure which disappeared after manipulation. The patient succumbed and autopsy revealed a paralytic ileus with emboli of the pulmonary artery. Henle expressed the opinion that the mechanism was caused by pulmonary emboli acting reflexly through the autonomic nervous system, thus causing a spastic ileus. A case noted by Brink<sup>2</sup> which occurred in a young patient was characterized by intermittent attacks of intestinal obstruction. Although fecal vomiting was not present in this case, the severe colicky pain with obstipation made him consider an organic factor as responsible in causing the obstruction. A spasm was subsequently observed in the region of the splenic flexure upon the introduction of barium. However, after waiting fifteen minutes and with manipulation, the barium trickled through. The case reported by Lichti<sup>9</sup> in which a 14-day-old infant was afflicted with an ileus is of unusual interest. X-ray seemed to demonstrate the lesion at the midtransverse colon, although post-mortem showed a constriction at the splenic flexure. The patient in Case 2, in whom a barium enema revealed an obstruction at the splenic flexure, was given a course of atropinization. The second x-ray series revealed a persistence of obstruction. Operation, however, did not reveal any pathology, the lesion undoubtedly being due to spasm. Case 3 is of unusual interest because the barium enema revealed an obstructing lesion at the splenic flexure. A preliminary cecostomy was performed as a decompressive measure. The obstruction appeared relieved. Subsequent barium enemas failed to reveal any lesion in the splenic flexure and accordingly the cecostomy was closed. The patient was last seen almost a year later and was in excellent condition.

The most commonly involved site of the large intestine subject to muscular spasm is either the descending colon or sigmoid, or both may be

patient was admitted with severe gastrointestinal symptoms in addition to neurotic symptoms. He received sulfarsphenamine injections and left the hospital after two months. A little more than two weeks after discharge he was brought to the hospital in a state of profound stupor. He seemed disoriented and would not eat. There had been constipation for several days, meteorism, and vomiting of greenish stomach contents. His pulse was good and there was no tachycardia. The abdomen was greatly distended and the "intestine stood out in relief." There was no visible peristalsis. Rectal examination was negative. A tentative diagnosis of mechanical occlusion in the colon or the sigmoid was made and laparotomy was performed under local anesthesia. The descending colon was found to be distended to the size of a forearm. Rapid digital exploration of the abdominal cavity disclosed no abnormal condition. A cecostomy was done. The meteorism passed off very slowly, and vomiting and eructations did not cease until several days after operation. Six days postoperatively, x-ray examination demonstrated normal passage and the absence of any obstructions in the colon. The neural symptoms persisted for six months. After discharge the patient resumed his usual occupation and did not seem to suffer from any functional disorder.

CASE 4.—(No. 417595.) This was the second admission of A. S., aged 64 years, admitted Dec. 8, 1937, and discharged Jan. 16, 1938, who had undergone a partial gastrectomy ten years before for prepyloric ulcer. He had apparently been free of all his previous attacks since operation. Eight months ago he had suffered an attack of precordial pain which had been diagnosed as due to coronary thrombosis. In the six days before admission the patient had noted generalized abdominal cramping pain, obstipation, and progressive vomiting and distention. Enemas had been ineffectual except for a slight amount of gas passed just before hospitalization.

Physical examination disclosed a somewhat emaciated, elderly white male. The pharynx was moderately injected with a marked postnasal drip. The chest was emphysematous but the lungs were clear. The heart was not enlarged. The sounds were of poor quality and slightly irregular. Blood pressure was 130/60. The abdomen was soft and moderately distended. Occasional peristaltic waves could be seen. There was a well-healed, midpigastic scar present and an easily reducible left hernia. Rectal examination was negative. Hemoglobin, 82 per cent; urea nitrogen, 1 mg. per 100 c.c.; sugar, 95; chlorides, 560;  $\text{CO}_2$ , 61.2; volume, 10; Wassermann, negative. Urine was negative except for transient acetoneuria. Electrocardiogram showed evidence of myocardial damage. X-ray of the abdomen showed marked dilatation of colon with gas and feces but no gas was demonstrated in the rectum. Barium enema examination showed an obstructing lesion in the midsigmoid about two inches in length which had the appearance of a neoplasm.

Soon after admission a right McBurney incision under local anesthesia was made. The cecum was enormously distended and a Kader type of valvular cecostomy was performed with a de Pezzer catheter. Postoperatively, the cecostomy drained well, the abdomen became less distended, and the pain diminished. Two days later he showed signs of myocardial infarction. Oxygen therapy was instituted and the condition improved sufficiently so that two weeks later he was re-explored under ethylene anesthesia. There was a large redundant sigmoid, a band of adhesions, and some indurated chronic inflammatory tissue on the mesenteric side of the colon, possibly due to diverticula. These pathologic findings may have reflexly produced a spasm of the sigmoid.

On the second postoperative day the patient developed irregular temperature, dyspnea, cyanosis, and signs of pneumonitis in the left lower lobe. With oxygen and supportive therapy this subsided and the postoperative care was uneventful. The wound healed well and cecostomy drainage gradually diminished. Rectal movements occurred spontaneously. Sixteen days postoperatively patient was discharged. He was readmitted Apr. 22, 1938, and discharged May 11, 1938, for an extraperi-

still showed no occlusion, and belladonna was continued. Meteorism was marked, but the patient could pursue his occupation. When a new roentgenogram taken at the end of six days showed no abnormality, the author ordered a barium enema. The rectum and sigmoid were easily filled, but at the junction of the latter with the descending colon the contrast medium could not proceed. When the pressure was greatly increased, the obstruction suddenly yielded and the barium spread through the colon. The enema produced immediate evacuation of large quantities of feces and gas but no blood. The abdomen resumed normal dimensions. A new x-ray examination on the following day disclosed no deformation of the intestine. Two weeks later, with intestinal function normal, disorders of surface and deep sensibility developed, and a paraplegia was diagnosed. Serologic examination indicated syphilis. The paraplegia disappeared on treatment. In the twelve-year period which elapsed since the patient came under observation, frequent follow-up examinations have shown no intestinal symptoms.

Lichter.<sup>9</sup> A male infant was seen two days after a normal birth. There was a history of vomiting of greenish stomach content. An extreme degree of meteorism was present. An enema induced an evacuation of meconium. X-ray examination showed an ectatic stomach and one-half hour later the barium particles in a horizontal direction were probably in the duodenum. The findings remained unchanged at the end of five hours. At operation the entire duodenum was found in a state of extreme spastic contraction, but under the eye of the surgeon the duodenum gradually returned to its normal condition. No other abnormality was noted in the gastrointestinal canal. The vomiting ceased after operation but recurred on the following day with greater violence. Several hours later the infant died with symptoms of aspiration pneumonia. Autopsy showed the small and large intestines greatly distended. The distal end of the sigmoid at the junction with the rectum was well contracted. Congenital megacolon. The cause of death was obscure. The disorder of motility in the small intestine was verified at operation and a similar finding in the sigmoid flexure was apparent from the post mortem report.

Sohn.<sup>24</sup> A female, aged 45 years, was admitted with a five-day history of obstipation. Two days before she suffered from eructations and then vomiting, first of the stomach content and later of feculent nature. She also complained of intermittent violent colicky pains. The attending physician referred the patient to the hospital with a diagnosis of ileus. Physical examination disclosed a nervous patient. Her temperature was normal and the pulse was accelerated. The pupils reacted promptly to light and in accommodation. There were no hysteric stigmas. Dermographism and exaggerated patellar reflexes. The abdomen was greatly distended and both lower quadrants were tender. Peristalsis was perceptible through the abdominal wall. Enemas were ineffectual. The diagnosis of mechanical ileus was confirmed, and operation was performed under ether anesthesia. The sigmoid flexure, of anemic appearance, was in a state of spastic contracture. A flat ribbon-like body was felt which was interpreted as being a tapeworm, but which proved to be a flattened scybal. The mucosa of the band was rather dry and there were no ulcers, no sign of inflammation, and no other foreign body visible. Two days later the contraction still persisted and a colostomy above the constricted area was performed. About a month later stools began to pass by the natural route. The patient was discharged two weeks later. The artificial anus was permitted to remain as a safety measure. She was readmitted eight months later for closure of the colostomy and discharged three weeks later cured.

Schaeffer.<sup>22</sup> A man, aged 37 years, previously healthy, suffered from recurrent disorders of subjective sensibility and paresthesias associated with parietic symptoms said to be of six years' standing. In some instances the symptoms were hemiplegic, in others monoplegic. They recurred once a year or more often, lasting from several weeks to several months. Recovery was always spontaneous. The

ureter were performed. The postoperative course was stormy. From the fifth day there was no flatus. From the sixth day on the patient complained of pain and tightness in the abdomen. Two or three enemas daily produced no bowel movements or flatus. On the eighth day the patient began vomiting, and fecal vomiting became apparent on the tenth day. The pulse was small (130 to 140). An exploratory laparotomy was performed on the tenth day. There were no peritonitis and adhesions. The colon descendens and sigmoid flexure were firmly contracted, resembling a rope the width of the little finger. The rectum was of normal width. A colostomy was performed and the patient was discharged thirty six days after the second laparotomy, but was reexamined at frequent intervals. She had no recurrence of her symptoms, and about three months later the colostomy was closed.

Pototschnig:<sup>20</sup> A soldier, aged 22 years, was on the way to the front. Following a large meal, he felt gastric and abdominal pain, complained of weakness, and began to vomit. There were no bowel movements. Spontaneous improvement occurred two days later. Four days later (six days after the onset) he was admitted with the same symptoms. A diagnosis of intestinal obstruction was made. Prior to operation the stomach was washed, producing a considerable amount of fluid stomach content mixed with undigested solid food and bile. The abdominal distention disappeared and the abdomen became soft. This development cast doubt on the first diagnosis, and either an acute dilatation of the stomach, or an arterio mesenterial occlusion of the duodenum was now considered. Rectal examination was painful. The pulse was rapid and of low tension. Exploratory laparotomy disclosed nothing abnormal with the exception of some circumscribed perityphlitic adhesions. An appendectomy was performed. The patient tolerated the operation well, and his condition on the following day was satisfactory. On the second day after operation there was a renewed attack of abdominal pain, the third since the onset, with vomiting. The patient rapidly deteriorated and died the following day. An autopsy was performed three hours after his death. About 50 cm. from the duodenojejunal flexure, there was an annular constriction of the small intestine, and in the sigmoid flexure, a similar constriction. Both could be effaced by simple traction of the intestinal walls. The mucosa was normal, and there was no ulceration or cicatrization.

While the pathology of the area involved shows very little as a rule, in the case reported by Biernath<sup>1</sup> the post-mortem examination revealed the distention of the bowel 25 cm. from the anus due to a stricture impassable even to the little finger. The mucosa was intact and appeared normal. The only pathology findings were several small diverticuli, one of which was adherent to the bladder. The involved area presented hypertrophy of the musculature over a segment of 5 cm. Microscopically there was no inflammation. The conclusion reached was that the condition represented an idiopathic hypertrophy of the intestinal musculature.

Biernath,<sup>1</sup> A male, aged 50 years, was admitted to the hospital with a tentative diagnosis of appendicitis. On admission the patient presented very marked symptoms of a chronic ileus but operation did not appear urgent. X-ray examination with bismuth enema indicated a stricture interpreted as carcinoma in the distal portion of the sigmoid flexure. The enema was evacuated the same evening. During the night the ileus became complete, but despite immediate operation, intestinal purities had advanced to such an extent that enemas given through the colostomy were ineffectual. The patient died. At post mortem a stricture impassable even for the little finger was discovered at a distance of 26 cm. (the report given in *Zentralbl. f. Chir.* 40, 1820, 1913, states 12 cm.) from the anus. The mucosa

toneal closure of the cecostomy under ethylene anesthesia. This postoperative course was uneventful. He was last seen on Dec. 6, 1939, and was well, although he complained of constipation which could only be relieved by cathartics.

**CASE 5.**—(No. 439833.) This was the first admission of F. Z., aged 71 years, an inmate of the Home for Aged, who for the past several years had had frequency of urination and occasional dribbling. He was admitted on May 3, 1939, and died on May 9, 1939. For the past thirty years he had had a chronic cough productive of a small amount of foul sputum. For six months he had had episodes of paroxysmal nocturnal dyspnea. For the past seven years he had had diabetes controlled by diet. Three weeks before admission the patient noticed swelling of the abdomen, and a week prior to admission he had severe abdominal cramps necessitating daily enemas which were effectual. Except for constipation he had no previous gastrointestinal symptomatology.

Physical examination disclosed a senile, undernourished male with evidence of recent loss of weight. Chest was emphysematous and both lung bases showed numerous coarse moist râles. The heart was not enlarged; there were no murmurs but extrasystoles. Blood pressure 158(?) / 70. Marked peripheral sclerosis. Abdomen was markedly distended and tympanitic except suprapubically, where the outline of a distended bladder was felt. Increased peristaltic sounds were audible. The liver was palpable two fingers below the costal margin. Rectal examination disclosed the prostate to be enlarged, firm, and slightly irregular. Urine showed specific gravity of 1.015; albumin, 1 plus; occasional W.B.C.; urea nitrogen, 29 mg. per 10 c.c.; sugar, 155; and chloride, 560. Wassermann was four plus. Flat plate of the abdomen showed marked distention of the large bowel and some distention of the small bowel. Barium enema was done and showed obstruction to the passage of barium in the region of the sigmoid with dilatation of the bowel above. However, since the actual site of the obstruction could not be demonstrated because satisfactory films were not obtainable, a positive diagnosis of neoplasm could not be made.

Because of the marked obstruction unrelieved by enemas, a tube cecostomy was performed under local anesthesia. In delivering the cecum into the wound, it was found to be distended, but immediately collapsed upon manipulation.

Following operation the patient did not do well, but developed signs of pulmonary congestion. His bowels moved following oxgall enemas through the cecostomy and his obstruction was relieved. He died five days after operation. The post-mortem disclosed that the cause of death was a bronchopneumonia. There was no pathologic lesion in the sigmoid, although there was definite dilatation of the sigmoid above an area below which the bowel was of normal diameter.

Spasm of the sigmoid, however, may act as the cause of a postoperative obstruction. Cases of this nature were noted by Pankow<sup>17</sup> and Pototsehnig.<sup>20</sup>

Pankow:<sup>17</sup> An unmarried female, aged 40 years, was admitted to the hospital for intense pain in the right side, accompanied by sweating, chills and vomiting, from which she suffered off and on for one and one-half years. There had also been gradual increase of girth and difficulty in urinating. (Conjunctival and pharyngeal reflexes were present, and patellar reflexes were not increased.) The patient had a sense of lassitude and complained that her legs were often swollen. She slept well and complained of neither headaches nor dizziness. The rectal examination disclosed a tumor of the uterus, the size of a man's head. The rectum was displaced to the left. A diagnosis of myoma uteri was made. Operation was attended with great difficulty and the mesocolon was torn away almost completely from the sigmoid flexure. The rectum was opened but immediately closed. The right ureter and kidney were dilated so that nephrectomy and excision of the right

Inasmuch as the diagnosis of a spastic ileus of the large bowel is rarely made, the therapy in these cases is usually that which is accorded to any patient suffering from an acute intestinal obstruction, that of surgical exploration. If the evidence is sufficient to suspect muscular spasm and if the patient is not too acutely ill, conservative therapy may be instituted for a time. If there is definite evidence by x-ray examination that the small intestine is dilated as well as parts of the large bowel, a decompression may be attempted by the passage of the Miller-Abbott tube. In the past, however, belladonna and external heat have been applied in an attempt to prove therapeutically that the lesion is due to spasm. This is not always successful, as demonstrated in Case 2, though successes have been obtained by the use of drugs. The majority of these cases have been explored, and it is from this surgical experience that our knowledge of the pathology of this unique condition has been gathered. If a definite spasm is recognized as causing the obstruction, and the resulting ileus and the distention are not too severe, nothing need be done, and the majority of these patients do well subsequently under conservative therapy, but in many cases the ileus has been so marked that definite decompression measures were indicated. Ileostomy, cecostomy, and colostomy proximal to the point of obstruction have often been life-saving measures. In the majority of instances these procedures have been done as preliminary measures in the belief that an actual obstructing lesion existed distally, without actually verifying its presence by further exploration at the time. It is, therefore, most important that before any subsequent operation is undertaken to remove a primary constricting lesion another series of postoperative x-rays be taken to verify the cause of the obstruction. This simple expedient may save the patient an unnecessary procedure. In Case 3, in which a malignancy was thought to be present, subsequent barium enemas revealed the fact that the so-called lesion had disappeared and was evidently the result of a spasm. Case 4, in which a malignant lesion of the sigmoid was suspected, was re-explored following a cecostomy. The exploration was practically negative. If another x-ray series had been taken, this patient might have been spared an unnecessary operation. The postoperative course in most of these patients is not particularly stormy. In Case 1, however, in which an organic lesion just distal to the cecum was suspected as a result of several x-ray examinations, operation revealed no intrinsic pathology and only the presence of a few adhesions. Postoperative course was characterized by a reflex ileus of such magnitude that evisceration took place. Following conservative therapy, however, this subsided and, since discharge, the patient has had no other attacks of obstruction, although the x-ray picture still shows a tendency to spasm in this area.

If either an ileostomy or cecostomy is performed, the tube may be withdrawn as soon as the normal bowel habit has been established. This

was intact, and no ulcerous or cicatricial processes could be seen. The only pathologic findings were several small diverticula, one of which was adherent to the bladder. The involved area presented hypertrophy of the musculature over a segment of 5 cm. in length. Tuberculosis, syphilis, and gonorrhea could be ruled out. Microscopically there was no inflammation, not even small-cell infiltration. The conclusion reached was that the condition presented an idiopathic hypertrophy of the intestinal musculature.

Several factors become quite evident after a study of these recorded cases. Both sexes appear equally susceptible. The age of onset of this condition is variable. It has been observed in infants, and, while the majority of cases have been in the third and fourth decades, the ages in our series were 48, 60, 71, 70, and 81 years respectively. This old-age group is especially interesting in view of the fact that many authors have emphasized the existence of a neurotic background, especially in the young. They stress that patients subject to this particular syndrome are, as a rule, of a hysterical type. While this is undoubtedly true in many instances, it cannot be universally applied.

The history obtained in these cases is similar to that obtained in any patient suffering from an intestinal obstruction. It has very little, if anything, to differentiate it from an ileus due to the other countless intrinsic and extrinsic lesions which obstruct the intestinal flow. The character, the intensity, and the type of pain, the degree of vomiting, the obstipation, and the extent of the abdominal distention vary as to the site of the lesion and as to the degree and the extent of the muscle spasm. The history may be either one of mild episodes of recurrent attacks of cramps and nausea, or it may be a severe attack of abdominal pain associated with persistent vomiting, at first gastric in character, then subsequently feculent. However, the physical examination as a rule does not disclose a patient too acutely ill. The abdominal distention is variable and intestinal erections with or without visible peristalsis may be present. The spastic bowel may occasionally be palpated as a hard, firm tumor. This finding, however, is subject to great variations, for the mass may entirely disappear at subsequent examinations or appear to migrate to other quadrants of the abdomen.

If any means at our present command were to be of aid in the differential diagnosis of this type of obstruction from one due to a stenotic malignancy, some help might be obtained by a careful study of colonic roentgenograms and fluoroscopy. The x-ray findings in these cases do not show the characteristic findings usually ascribable to a malignancy. An immediate obstruction to the flow of a barium enema is usually apparent. However, with a little care and skillful manipulation, the spasm may relax and the barium pass freely into the remainder of the large bowel. In two of our series a colonic obstruction was noted, but the roentgenologist stated that the appearance was not characteristic of the type usually produced by the presence of a malignancy.

# EMERGENCY LAMINECTOMY FOR ACUTE EPIDURAL ABSCESS OF THE SPINAL CANAL\*

REPORT OF FOUR CASES WITH RECOVERY IN THREE

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**A**CU TE epidural abscess of the spinal canal is an important though little known disease which needlessly kills many people every year. Statistical proof of this statement is lacking, but convincing evidence of its veracity will be presented here. As was true in the case of pyogenic abscess of such organs as the lung, brain, and liver, reiteration will be necessary to make physicians aware of the disease. Moreover, it is even more important to make an early diagnosis of abscess within the spinal canal than it is in the case of abscess of the various organs. An extradural abscess within the spinal canal rapidly produces paralysis of the legs and urinary bladder. Failure to drain these abscesses within a few hours after paralysis and anesthesia of the legs have become complete results in permanent paraplegia, if not death.

The clinical picture of acute epidural abscess of the spinal canal is constant enough to insure recognition if the disease is kept in mind. A patient who is recovering from multiple boils on the buttocks or elsewhere begins to have an unexplained fever. At about the same time he complains of severe pain in the back which radiates to one or both sides of the thorax. Within a few days the legs become weak and cutaneous sensation below the level of the pain diminishes. Fever continues, leucocytosis is demonstrable, and the spine becomes exquisitely tender. Within forty-eight hours of the onset of weakness the legs become completely paralyzed and urinary retention develops; shortly after, all forms of sensation below the level of the lesion are lost. If surgical treatment is not employed at this stage or sooner, the patient dies from extension of the infection, ascending pyelonephritis, or pyemia. If, on the other hand, the presence of an abscess in the spinal canal is suspected shortly after the onset of paralysis, the diagnosis may be verified by spinal puncture. Demonstration of a spinal fluid block indicates that the patient has an extradural abscess and not an infection of the cord itself. The surgical removal of a mass of pus and granulation tissue relieves the compression of the spinal cord and its blood supply. The degree of residual paralysis, if any, depends upon the degree of irreversible change produced in the spinal cord by compression and ischemia.

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may vary from a few days to weeks. For some unknown reason these spasmodic episodes are not apt to recur following operative intervention and the majority of these patients who have been followed for years remain well.

### SUMMARY

The etiological factors, the pathology, the clinical history, the physical findings, and the operative procedure in cases of intestinal obstruction due to spasm of the colon are discussed. Cases from the literature are briefly abstracted and five new cases are reported in detail.

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Examination divulged a temperature of 101° F., stiff neck, abdominal distention and tenderness, spastic paresis of the lower limbs, and diminished sensation below the level of the xiphoid process. Spinal puncture the day after admission produced clear fluid containing only one cell per cubic millimeter. Compression of the jugular veins caused no rise in the pressure of the fluid. By the next day complete flaccid paralysis of the legs had developed. A diagnosis of epidural spinal abscess was made and a neurosurgical consultation requested. The spinal puncture was repeated, the spinal block was verified, and 1 c.c. of lipiodol was injected into the subarachnoid space. Under the fluoroscope, with the head of the table lowered, the lipiodol was seen to stop at the level of the fifth dorsal vertebra.

Operation under local anesthesia was performed immediately, the fourth, fifth, and sixth dorsal spinous processes and laminae being removed. Pus escaped before the bone removal was completed. Two separate pockets of pus were found, each containing 1 c.c. A layer of granulation tissue occupying the epidural space was removed as completely as possible. The wound was loosely packed with strips of vaseline gauze. Culture proved the organism to be nonhemolytic streptococcus.

The patient gradually improved postoperatively with eventual subsidence of fever and by the seventeenth postoperative day could move his legs slightly. Physical therapy was instituted. By the twenty-eighth postoperative day the patient was able to walk short distances with crutches. He was discharged in fair health on Oct. 10, 1939, after fifty-nine days in the hospital. Four months later on Feb. 12, 1940, anesthesia had completely disappeared and the bladder function was practically normal. He is now walking with the aid of a cane and has returned to work in a newspaper office.

CASE 3.—E. C., a white man, aged 22 years, was admitted to Charity Hospital in New Orleans, Dec. 5, 1939, complaining of boils on the buttocks. These lesions had appeared about sixteen days prior to admission and had been incised.

The patient was acutely ill, as evidenced by a flushed face, clouded sensorium, fever, tachycardia, and rapid respiration. A diagnosis of *Staphylococcus aureus* septicemia was made by means of blood culture and the patient was given staphylococcal antitoxin, blood transfusions, and 2-(*p*-aminobenzenesulfonamido)-pyridine (sulfapyridine). He gradually improved and was practically ready to go home when, on Jan. 9, 1940, he experienced severe pain in the regions of the midthoracic spine and the sternum. The temperature on that day reached 100.6°. During the next two days the legs became paralyzed, sensory perception below the xiphoid process diminished, and catheterization of the urinary bladder became necessary. Tenderness pervaded the region of the sixth dorsal spinous process. The white blood cell count rose to 19,400. Spinal puncture with jugular compression showed a complete subarachnoid block. Fluoroscopy following the instillation of 0.5 c.c. of lipiodol indicated that the lower border of the block was at the seventh dorsal vertebra.

A few hours later under general anesthesia an incision was made with the electrosurgical knife. The spines and the laminae of the fourth through the seventh dorsal vertebrae were removed. Pus escaped from the epidural space as soon as the ligamentum flavum was opened. The granulation tissue encountered was so tenacious and vascular that nearly one and one-half hours were required to obtain adequate exposure of the dural sac.

Immediately prior to operation the patient was totally paralyzed except for slight movement in the toes of the left foot. A few days after operation he could move both legs without difficulty; he urinated voluntarily on the ninth day. When last examined four months after operation the patient was entirely well except for slight weakness of the right lower limb. The bladder and bowel were functioning normally and he was entirely free from pain or other complaints.

Because of past efforts, particularly of Weilbaecher,<sup>1</sup> the interns and residents at Charity Hospital in New Orleans recently became alert to the existence of this disease entity. This undoubtedly accounts for the surgical treatment of four such cases by me within a period of one year. All four of the patients were practically totally paralyzed prior to laminectomy. Three are now able to walk and have control of the urinary bladder. The other patient died from empyema. The report of these four cases follows:

CASE 1.—H. P., a white boy, aged 7 years, was admitted to Charity Hospital in New Orleans, Feb. 3, 1939, complaining of pain in the lower part of the chest.

Nearly three months before the patient had furuncles on the lips, thigh, wrists, and back. Two weeks before entering the hospital he was put to bed following a head cold because of severe pain in the lower thoracic spine which radiated to the front of the chest. Five days before admission the boy complained of weakness of the legs. During this illness he had a temperature varying from 99 to 102° F. When the patient was admitted to the hospital, his legs were too weak to permit standing and he was unable to urinate. The temperature was 100° F., the pulse rate 115, and the white blood cell count numbered 16,350. A tentative diagnosis of acute anterior poliomyelitis was made. By the third day paralysis of the legs became complete. The ankle jerks could be obtained, but the patellar reflexes were absent. The Babinski sign was present bilaterally. There was practically complete anesthesia below the level of the umbilicus. A neurosurgical consultation was requested. Fluoroscopy following the injection of 1 c.c. of lipiodol into the lumbar subarachnoid space demonstrated a complete spinal block at the level of the tenth dorsal vertebra. Nearly eighteen hours later at operation under local anesthesia numerous small pockets of pus were found in the epidural space. The epidural fat was hemorrhagic and edematous and invaded with granulation tissue. The infected material was removed, thus exposing the dural sac for a distance of about 10 cm. The sac began to pulsate. A rubber drain was laid in the wound and the skin was partially closed. The bacteriologist reported the *Staphylococcus albus* in the pus.

By the sixth postoperative day the patient moved the left leg and the toes of the right foot. The wound drained for several weeks before healing. Physical therapy was instituted and eventually the patient could walk unaided. The child was fitted with a back brace and discharged from the hospital on the one hundred and sixth postoperative day. In the fall, still wearing the brace, he was able to attend school. He was again seen on March 19, 1940, at which time examination disclosed a spastic paresis of the legs. He walked with a waddling gait, bending slightly forward and swaying from side to side. There were no sensory disturbances and the bladder and bowel functioned normally.

CASE 2.—G. M., a white man, aged 31 years, was admitted to Charity Hospital in New Orleans, July 14, 1939, complaining of pain in the chest, abdominal cramps, weakness of the legs and malaise.

Two months before admission the patient had had an attack of influenza, which was followed by slight deafness and pain in the right ear. On June 25 a mastoidectomy was performed. Convalescence was uneventful until July 10, when, following exposure to rain, he experienced pain in the lower part of the chest on the right side. On the day of admission the legs were weak and stiff and the bladder was paralyzed.

\*Case 1 has been previously reported by Weilbaecher.<sup>1</sup> Cases 2 and 3 appeared in the June, 1940, issue of the *New Orleans Medical and Surgical Journal* as case presentations before the Orleans Parish Medical Society.

*Location.*—An understanding of the anatomy of the epidural space helps but does not entirely succeed in explaining why these abscesses localize in certain parts of the spinal canal. The spinal epidural space, which is filled with fat, loose areolar tissue, and blood vessels, is located on the dorsal and lateral aspects of the dura. Ventral to the spinal nerves the dura is closely applied to the bodies of the vertebrae and their ligaments so that the epidural space on the anterior aspect of the cord is only a potential one. This is true from the first cervical vertebra to the second sacral segment; below this point the epidural space surrounds the dural sac.

The epidural space is not uniform in size throughout its length. This was observed by Dandy,<sup>6</sup> who, in 1926, made an investigation of the subject. In its upper portion, the cervical region, the space is only potential. The epidural space really starts at the seventh cervical vertebra, gradually increasing in size until it reaches the middle third of the dorsal spine and tapering off slowly until it is quite shallow between the eleventh thoracic and second lumbar vertebrae. Between the second lumbar and the sacral vertebrae the epidural space involves the largest area.

It has been noted that these abscesses, with few exceptions, are located posteriorly. However it is not only anatomically possible for epidural abscesses to occur in the anterior part of the vertebral canal, but five such cases have been reported.<sup>9, 24-26</sup> Most abscesses localize in the thoracic region. Why they do not occur more frequently in the larger lumbar and sacral epidural spaces is not definitely known, but the fact is possibly related to the vascular supply of these regions. Although some of these infections become circumscribed, others have been known to extend the length of the epidural space (Weillbaccher's second case and others).

*Etiology*—Infections in the epidural space may occur by direct extension from suppuration in adjacent tissues or by metastasis from a distant focus through the blood or lymph streams. Most of these abscesses arise by metastasis through the blood stream from furuncles of the skin, as in my first, third, and fourth cases. Boils, which are probably the commonest source of infection in this disease, were the etiologic factor in 32.6 per cent of the cases reported by Gasul and Jaffe<sup>7</sup> in their series collected from the literature. My second case was apparently metastatic from purulent mastoiditis. Mixer and Smithwick<sup>8</sup> also reported a case with a similar history. The source of the organism was not known in 17.9 per cent of Gasul and Jaffe's collected series, but there was a history of trauma in these cases. Hunt,<sup>27</sup> Donati,<sup>28</sup> Schönwerth,<sup>29</sup> and Browder and Meyers<sup>37</sup> believe that almost every epidural suppuration occurs secondary to osteomyelitis of a vertebra. They contend that the bone focus is usually unrecognized at operation or necropsy. That so

CASE 4.—E. C., a white man, aged 18 years, was admitted to Charity Hospital in New Orleans, June 30, 1939, complaining of pain in the chest. The patient gave a history of a recent boil on the elbow. One week before admission he felt a sharp pain in the back of the chest. On June 25 severe frontal and occipital headache appeared. The day before admission he experienced difficulty in moving his legs. On the day he entered the hospital, he could not move the legs at all and could not void.

Examination disclosed flaccid paralysis of the lower limbs, diminished sensation below the level of the xiphoid process, and a distended urinary bladder. Fever and leucocytosis were demonstrable. The spinal fluid was clear. Queckenstedt's test was not performed.

A neurosurgical consultation was requested on the following day. Spinal puncture revealed a complete block. Tenderness and redness extended over the fifth, sixth, and seventh spinous processes. Anesthesia and paralysis below this level were complete. Although the prognosis was considered to be practically hopeless, laminectomy was immediately performed under general anesthesia. Pus was found in the paravertebral muscles as well as in the epidural space. The offending organism was *Staphylococcus albus*. The laminectomy wound eventually granulated in and epithelized but the patient died of empyema on the seventy-sixth postoperative day.

*Incidence.*—The incidence of epidural spinal abscess is not known, but, according to Hirschfeld and Yaskin,<sup>2</sup> the disease was recognized in Italy as early as 1820 by Bergamaschi.<sup>3</sup> The literature was reviewed in German by Schmalz<sup>4</sup> in 1925; in French, by Veraguth and Schnyder<sup>5</sup> in 1929; and in English, by Dandy<sup>6</sup> in 1926, Gasul and Jaffe<sup>7</sup> in 1935, and Campbell<sup>8</sup> in 1937. In 1926 Dandy<sup>6</sup> stated that he had never seen a patient with an abscess of the extradural space either during life or at necropsy but that he had been able to collect twenty-five cases which had appeared sporadically in the literature up to that time. In 1935 Gasul and Jaffe<sup>7</sup> collected sixty-four cases from the literature and added three of their own. It is noteworthy that in only a few textbooks is the condition mentioned. At first glance these facts suggest that the disease is rare. However, there are sufficient reasons to believe that not the disease but its recognition and surgical treatment are rare. This is attested by the fact that, although Weilbaeher<sup>1</sup> was able to find only one case from a search of the records at Charity Hospital in New Orleans for the period from 1906 to 1937, seven cases have been recognized since then. Further evidence that the disease probably occurs relatively frequently is indicated by the fact that Mixter and Smithwick<sup>9</sup> have personally observed ten cases. Certainly many children and adults develop transverse myelitis every year. Probably some of the cases which are diagnosed clinically as poliomyelitis, infectious myelitis, syphilis of the spinal cord, spinal meningitis, and apoplexy of the cord are in reality cases of metastatic epidural spinal abscess. Since Gasul and Jaffe<sup>7</sup> reviewed the literature in 1935, scattered reports of cases have appeared with increasing frequency.<sup>2, 8, 10-23</sup>

ous procedure. When the abscess is somewhere in the thoracic region, little risk is attached to lumbar spinal puncture. If the Queckenstedt sign can be demonstrated, in all probability one is not dealing with extradural suppuration. When a block exists, extradural suppuration is almost certainly present. In such a case it is helpful to inject 0.5 c.c. of lipiodol into the canal before withdrawing the needle. The patient may then be put on the tilting fluoroscopic table and the head lowered. The lipiodol will gravitate to and stop at the lower border of the lesion. This additional information is often useful. The sensory examination tells the upper level of the lesion; the lipiodol indicates the length of the lesion. In short, it is possible for extradural suppuration to compress the dural sac over a large area. The spinal fluid may be clear; often it is cloudy because of pleocytosis. Organisms in the fluid indicate that meningitis is complicating the extradural infection.

*Treatment.*—Once the diagnosis of compression of the spinal cord has been established, laminectomy with drainage must be done at the earliest possible moment. A longitudinal incision is made over the posterior spinous processes and the muscles of the back are retracted so that three or four posterior spinous processes are isolated. Two spines nearest the center of the wound are removed. One of the neural arches is then taken off and the ligamentum flavum opened. Pus and granulation tissue are immediately encountered. The laminectomy is then carried both upward and downward until the poles of the lesion are reached. Whether two or ten laminae are removed is not a matter of consideration. The granulation tissue may lie on the posterior surface of the dural sac or may lie as well on both lateral surfaces. Fortunately, the pyogenic tissue rarely lies anterior to the dural sac. When the operator has reached the upper pole of the lesion, the entire dural sac will begin to show normal pulsations. It is not necessary, nor indeed possible, to remove all of the pyogenic tissue from the spinal canal. The object of the operation is to decompress the dural sac and to provide adequate drainage of the extradural space. A soft rubber drain may be laid on the surface of the dura or the wound may be loosely packed with strips of vaseline gauze. In a few weeks the wound granulates in from the bottom and epithelizes.

*Prognosis.*—According to Campbell,<sup>8</sup> four cases of recovery from metastatic epidural spinal abscess without operation have been reported (Leydon,<sup>9</sup> Keienburg,<sup>10</sup> Braun,<sup>11</sup> and None<sup>5</sup>). Recovery in Keienburg's patient followed the injection of trypanflavin. That certain metastatic infections in the epidural space are self-limited and do not progress to the stage of compressing the cord and causing paralysis is a plausible explanation for recoveries without surgical intervention. When the diagnosis is made before paralysis is complete or before paralysis has been complete for more than a few hours, there is good chance for complete

few spinal abscesses are found adjacent to the vertebral bodies (anterior to the dorsal sac) and that so few occur in the cervical and sacral regions are arguments against this theory.

The organism most often responsible for this infection is the staphylococcus, which was the offending organism in every case in Gasul and Jaffe's series in which a bacteriologic examination was reported, except the case of Delearde,<sup>30</sup> which was caused by the streptococcus, and that of Schick,<sup>31</sup> caused by the pneumococcus. The staphylococcus organism was responsible for the infection in three of my four cases. The other case was a nonhemolytic streptococcal infection. Raney<sup>32</sup> reported three cases and Browder and Meyers,<sup>25</sup> one case, in which culture proved the organism to be the pneumococcus. Raymond and Sicard<sup>33</sup> had a case caused by the typhoid bacillus and Campbell<sup>8</sup> reported a case with *Bacillus pyocyaneus* infection.

*Diagnosis.*—It is unreasonable to hope to make consistently a diagnosis of metastatic abscess of the spinal canal before symptoms of spinal cord damage appear, although Cohen<sup>34</sup> and Slaughter and associates<sup>35</sup> reported cases in which the diagnosis was made before the appearance of neurologic signs. If a patient with a history of boils should begin to have severe root pain in the back, one could suspect the presence of spinal suppuration and could be alert to the development of weakness of the legs. However, the rapid development of weakness of the lower extremities suggests a number of diseases. If the patient is afebrile, such conditions as metastatic tumor of the spinal canal, compression of the spinal cord by tumor of the vertebrae, Pott's disease, and hysteria are considered. If fever is present, the most likely possibilities in addition to epidural abscess are poliomyelitis and infectious myelitis. In addition to other characteristic clinical findings, the patient with poliomyelitis or infectious myelitis will not have a block upon performance of Queckenstedt's test. In brief, if the patient has fever, rapidly progressing weakness of the legs, and a spinal block, it is certain that the diagnosis is compression of the spinal cord by extradural suppuration. Whether the suppuration is by metastasis or by direct extension is of no immediate significance. A surgical emergency exists and prompt decompressive laminectomy is mandatory.

The level of the lesion can be determined by clinical examination. The sensory level is usually fairly definite. The level of root pain is a still more accurate indication of the site of the lesion. Tenderness of the spine on palpation is also informative. When the symptoms are suggestive of an abscess in the lumbar spinal canal, it is unwise to do a spinal puncture. If one failed to aspirate pus from the extradural space, the point of the needle would undoubtedly be carried into the subarachnoid space and meningitis could result. Several authors have advocated attempting to aspirate pus from the extradural space, but this is a danger-

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or partial recovery of function following decompressive laminectomy and drainage. Of the sixty-seven cases collected by Gasul and Jaffe, thirty-five had laminectomies, 48.7 per cent of which recovered. Abrahamson and co-workers<sup>38</sup> observed that, in a collected series of sixty cases, twenty of the thirty patients who had operations survived, giving a mortality of 33.3 per cent; whereas, the mortality rate for the thirty patients who were not treated surgically was 100 per cent. Campbell<sup>8</sup> estimated that about 40 per cent of all patients surviving operation have complete restoration of function. If the diagnosis is delayed until paralysis has been complete for a number of days, operation is usually contraindicated. However, in certain instances of this type, operation will be performed to relieve the severe root pain and to drain the supuration so that it will not extend into the abdominal or thoracic cavities. Such a procedure might save the patient's life for the time being, but the total paraplegia would persist and death would merely be delayed.

In three of the four cases reported in this paper, operation was performed just before or shortly after paralysis had become complete. These three patients are now able to walk and have control of the anal and vesical sphincters, but there are residual motor disturbances. The other patient, who had been paralyzed nearly forty-eight hours before operation, died of empyema.

#### SUMMARY

1. Early recognition and prompt drainage of acute epidural abscess of the spinal canal is urged.

2. The incidence, location, etiology, diagnosis, treatment, and prognosis of epidural spinal abscess are discussed.

3. Four cases of acute epidural spinal abscess, three of which recovered following decompressive laminectomy, are reported.

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phlebitis, puerperal sepsis, and appendicitis. At some time during the first two or three months following the infection and often within the first two weeks, the patient begins to complain of a boring pain in a circumscribed part of the vertebral axis. The pain is annoying, constant, at times throbbing, made more intense by coughing, sneezing, and any movements of the spine, and is frequently associated with tenderness over the painful area. Localized swelling may be present. There may be complaints of chilly sensations, headache, lassitude, generalized myalgia, feverishness, and sweating, all of which may rapidly recede or may persist for several weeks. The temperature may range between 101 and 105° F. and later establish itself as of the septic type. Corresponding acceleration of the pulse and respiratory rates is often present. The blood count reveals a polymorphonuclear leucocytosis of from 12,000 to 35,000 per cubic millimeter. Commonly, after several days there is added to the boring pain in the back a radicular type of pain, sharp, often lancinating, and frequently associated with a "girdle sensation." The neck may become rigid. Headache and vomiting may ensue. In some instances the infection is fulminating in character and may be complicated by septicemia and this in turn by metastatic implication of lungs, heart, liver, and kidneys. Neurologic manifestations, although they may be present, do not become prominent in some cases before death ensues. In the average case, however, the infection remains more localized and the involvement of the spinal cord or cauda equina is slowly progressive, until at the end of four or five days complete interruption of their physiologic functions supervenes. During the early phase of implication of the spinal cord, paresthesias and dysesthesias of one or more extremities often presage the more dramatic and later appearing signs. Examination at this time frequently discloses a marked degree of cutaneous sensitivity to painful stimuli over the affected parts. A degree of paralysis of the musculature below the level of the lesion soon makes its appearance. Rapid implication of the spinal cord usually results in flaccidity and areflexia, irrespective of the level involved: whereas, in the subacute and chronic forms spasticity and hyper-reflexia are more commonly observed. Involvement of the lower lumbar and sacral segments of the cord and the cauda equina regularly results in flaccidity and areflexia. Varying degrees of abdominal distention and tympany are frequently encountered. The urinary bladder becomes distended, followed by overflow incontinence. Fecal incontinence may shortly ensue. The sensory status, like the motor, is dependent upon the acuteness of the process and the degree of involvement of the spinal cord and nerve roots. In some instances acrognosis and pallesthesia have been observed to persist longer than the superficial modalities of sensation. In others preservation of the appreciation of painful and thermal stimuli with loss of the proprioceptive sensibilities has been demonstrated. Trophic alterations of the skin are frequently

# PYOGENIC INFECTIONS OF THE SPINAL EPIDURAL SPACE\*

## A CONSIDERATION OF THE ANATOMIC AND PHYSIOLOGIC PATHOLOGY

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IN 1936 a review of the literature concerning pyogenic infections of the spinal epidural space disclosed 203 cases to which we added 7.<sup>1</sup> Our interest in this subject has been augmented by experience with a second group of 7 instances of this disease. During the past four years several important contributions<sup>2-7</sup> have emphasized the clinical aspects of this entity. In spite of this it would seem that the syndrome is still not generally recognized, as is indicated by the fact that 6 of the 7 recently encountered cases did not come under our observation until the disease was so advanced that application of appropriate therapy came too late to effect recovery. The present communication is intended to correlate the clinical features of acute pyogenic epidural infections with the concomitant pathologic alterations and to describe the histologic changes observed in the spinal cord and their probable relations to the pathologic physiology associated therewith.

It has been quite generally considered that there are two modes by which septic agents may invade the spinal epidural space. In the first of these it is regarded that the infection extends directly from an inflammatory process in tissues adjacent to the vertebral column into the epidural space. In the second mode of invasion it is presumed that a septic metastasis arises from some more distant focus of infection and by a hematogenous route establishes itself directly in the epidural space. Numerically the cases included in the first group are in the minority and these present the lesser difficulty of pathogenic interpretation. It is with the generally accepted pathogenesis of the second group that we are at variance. The convictions expressed in our earlier communication, namely, that all such lesions are preceded by vertebral osteomyelitis, appear under no necessity of revision in the light of the present study.

Although the clinical picture has been amply described in several reports, it seems advisable to recapitulate. Once familiarity with the entity has been gained, the story and clinical findings should leave little doubt regarding the diagnosis, especially in the acute form of the disease. The history is usually positive for a previous or coexistent infection. Representative examples of such infections are nasopharyngitis, otitis media, tonsillitis, abscess of tooth, pneumonia, furunculosis.

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7. Abscess of tooth extracted, acute upper respiratory infection	1 wk	3 mo	Weakness of lower extremities	T3	<i>Staphylococcus aureus</i>	Yes, twice, 1935 and 1934	Recovered
8. Infected finger	2 wk	1 mo	Urinary difficulty, weakness of lower extremities	T5-T6	No culture, wound healed primarily	Yes	Recovered; partial collapse of a vertebra
9. Acute respiratory infection	16 days	12 days	Generalized twitching	L5	Blood culture positive for <i>Staphylococcus albus</i> ; gram positive coccus from abscess at L5; pneumococcus in cerebro-spinal fluid	No	Died 6 days after onset of pain in back
10. Tooth extracted; abscess of neck; osteomyelitis of jaw	8 mo.	11 days	Spasticity of right lower extremity	L2-L3	<i>Staphylococcus aureus</i>	No	Died 16 days after onset of pain in back
11. Abscess of tooth	5 days	5 days	Weakness of lower extremities	C1	<i>Staphylococcus aureus</i> and septicemia	Yes	Died 12 days after onset of pain in back
12. Furuncles of forearm	10 days	4 days	Urinary incontinence	T7-T8	<i>Staphylococcus aureus</i>	Yes	Recovered; 10 months paraplegic
13. Infected wound of scalp	3 mo. and 12 days	2 days	Weakness of left lower extremity	T8	<i>Staphylococcus aureus</i>	Yes	Recovered; slow restoration of function
14. Infection of back	12 yr., 8 mo., and 7 days	7 days	Urinary difficulty	T6	<i>Staphylococcus aureus</i>	Yes	Died 12 days after onset of pain in back

TABLE I  
SALIENT FEATURES OF 14 CASES OF SPINAL EPIDURAL INFECTION

PRIMARY LESION	TIME ELAPSED BETWEEN ONSET OF PRIMARY INFECTION AND PAIN IN BACK	TIME ELAPSED BETWEEN ONSET OF PAIN IN BACK AND NEUROLOGIC SIGNS	INITIAL NEUROLOGIC SIGN	VERTEBRAL LEVEL OF SPINAL LESION	ORGANISM	OPERATION	AUTOPSY	RESULT
1.* Acute upper respiratory infection	1 wk.	1 wk.	Urinary retention	L3	<i>Staphylococcus aureus</i> and nonhemolytic streptococcus	No	Bony destruction left lamina L3; pus in epidural space T2-L5	Died 5 wk. after onset of pain in back
2.* Abortion followed by uterine infection	6½ wk.	5 days	Urinary retention, spasticity right lower extremity, nutcheal rigidity	T3	<i>Staphylococcus aureus</i>	No	Osteomyelitis right lamina T3; pus in epidural space C5-L4	Died 18 days after onset of pain in back
3.* Acute respiratory infection and acute tonsillitis	1 days	1 days	Paresis right lower extremity	C7	<i>Staphylococcus aureus</i>	No	Destruction of right posterior part of centrum C7; abscess, C7-T2	Died 9 days after onset of pain in back
4.* General furnculosis	7 mo. (†)	27 days	Bilateral hyperreflexia, Babinski's sign	Osteomyelitis head of the left sixth rib	<i>Staphylococcus aureus</i>	Yes		Recovered
5.* Trauma to spine; no infection admitted	3 days	19 days	Paresthesiae both feet	T2-T3	Not reported	Yes		Recovered; residual urinary bladder dysfunction; slight spasticity of lower extremities
6.* Acute upper respiratory infection; pneumonia	Indefinite	Indefinite	Inability to extend left hand and wrist	C5	<i>Diplococcus lanceolatus</i>	Yes	Osteomyelitis C5	Died

\*Cases previously reported

cases thick creamy pus welled up from the paravertebral region upon retraction of the muscles. The pathologic changes in the epidural space ranged in character between two extremes, free pus and a circumscribed low-grade granulomatous mass. Between these extremes many intermediate grades were observed. The cephalad and caudad limits of the purulent collections were demarcated by a firm, well-vascularized, thickened epidural fat. In the more central portions of the lesions the fat was found in varying degrees of disintegration, ranging between early necrosis and complete liquefaction. The granulomas were represented as fairly discrete lesions. In length they extended a distance of over one to four vertebral segments, occupying the epidural space and conforming roughly to its shape. The greatest thickness ranged between 4 and 6 mm. and was most often discovered at the central portion of the involved area. From here the lesions tapered toward their periphery. On gross inspection the masses appeared grayish red and granular on the surface. No large blood vessels were visible. On section the granulomas were dense and intimately fused with the dural surface so that efforts to strip the lesions away from the dura were beset with the danger of tearing the latter. The superficial appearance of these lesions closely simulated that of other granulomas (syphilitic and tuberculous) and in certain cases that of lymphomatoid diseases of the spinal epidural space. The discovery of punctate areas of pus on the cut surface of such a mass greatly facilitated the differential diagnosis. However, in an occasional instance the diagnosis was not only impossible by gross inspection but exceedingly difficult even by microscopic examination. In Case 7 several well-qualified pathologists interpreted the microscopic findings as those of Hodgkin's disease and only after eleven years had elapsed could the issues be decided in favor of pyogenic granuloma. The dura itself was commonly but not invariably thickened adjacent to the epidural lesions. Microscopically the collagenous bundles of this structure were edematous and infiltrated with inflammatory cells. New capillaries and capillary tufts were abundantly in evidence. Some of the larger vessels were occluded by organized thrombi. Punctate abscesses were sometimes observed within the dura itself. In one instance the subdural space immediately underlying the lesion was occupied by a layer of amorphous cellular detritus. The leptomeninges appeared regularly to be implicated by the inflammatory process to a variable degree. In the very mild reactions of the piaarachnoid the cerebrospinal fluid appeared clear and colorless and often revealed an increased total protein content without pleocytosis. As a later complication the subarachnoid space of the entire cerebrospinal axis was implicated by a bacterial meningitis. More commonly, however, a limited portion of the subarachnoid space corresponding to the epidural lesion was obliterated. Here was demonstrable an outpouring of inflammatory cells and such an organization of mesoblastic elements as to fuse the arachnoid and the pia. The most

observed. Lumbar puncture in the average well-established case yields characteristic findings. The Queckenstedt test usually indicates the presence of complete or incomplete occlusion of the spinal subarachnoid space. The spinal fluid may vary in appearance from colorless to distinct xanthochromia and is commonly found to contain an increase in cells of from 50 to 100 per cubic millimeter. Lymphocytic cells are usually predominant. The protein content of the fluid is frequently increased to 50 mg. or more per 100 c.c. Culture and smear are negative for the presence of organisms unless the leptomeninges have been invaded. In some cases of the present series the inflammatory process was caudad to the conventional level for puncture and the possible presence of a subarachnoid block therefore could not be detected. In one patient with cervical cord involvement (Case 11) the subarachnoid space was found to be patent and the cerebrospinal fluid normal. In instances in which the lumbar epidural space is suspected of being the site of the suppuration, pus may be encountered during the performance of the lumbar puncture if frequent aspiration is carried out as the needle traverses this space.

It is rare to find roentgenographic evidence of bony changes of the vertebral column. In the present series of 14 cases there was a definite zone of bony destruction demonstrated by the roentgen-ray examination in one patient and by suggestive changes in another. Failure to identify a zone of bone destruction should not render one reluctant to make a diagnosis of spinal epidural infection. The important features bearing reference to the 14 cases included in this series are summarized in Table I.

*Pathology.*—The pathologic descriptions which follow are based on findings disclosed at operation in 9 instances together with necropsy data derived from 7 of the 8 patients who died. Among the 14 cases of the present series, gross evidence of osteomyelitis was demonstrable in 12 instances. This lesion was identified in 7 of the 12 cases at autopsy, in 2 at operation, and in the remaining 3 by its presence as suggested by the roentgenograms. In the remaining 2 cases the data were insufficient to exclude the possibility of the presence of this lesion. The gross and microscopic features of the vertebral osteomyelitis were in no essential respects different from osteomyelitic processes encountered in other bones. Upon approaching the vertebral column at operation or at autopsy, gross alterations of the soft tissues were occasionally observed before the bony column was reached. In 3 cases the muscles and fasciae were edematous to such a degree that an externally visible and palpable swelling was produced. In 2 of these incision disclosed free pus diffusely distributed in the fascial planes. The exposed vertebra affected by osteomyelitis revealed a shaggy, sometimes fenestrated periosteum which stripped with inordinate ease. The implicated bone was soft and when bitten with the rongeur exuded pus from its medullary portion. In 4

cases thick creamy pus welled up from the paravertebral region upon retraction of the muscles. The pathologic changes in the epidural space ranged in character between two extremes, free pus and a circumscribed low-grade granulomatous mass. Between these extremes many intermediate grades were observed. The cephalad and caudad limits of the purulent collections were demarcated by a firm, well-vascularized, thickened epidural fat. In the more central portions of the lesions the fat was found in varying degrees of disintegration, ranging between early necrosis and complete liquefaction. The granulomas were represented as fairly discrete lesions. In length they extended a distance of over one to four vertebral segments, occupying the epidural space and conforming roughly to its shape. The greatest thickness ranged between 4 and 6 mm. and was most often discovered at the central portion of the involved area. From here the lesions tapered toward their periphery. On gross inspection the masses appeared grayish red and granular on the surface. No large blood vessels were visible. On section the granulomas were dense and intimately fused with the dural surface so that efforts to strip the lesions away from the dura were beset with the danger of tearing the latter. The superficial appearance of these lesions closely simulated that of other granulomas (syphilitic and tuberculous) and in certain cases that of lymphomatoid diseases of the spinal epidural space. The discovery of punctate areas of pus on the cut surface of such a mass greatly facilitated the differential diagnosis. However, in an occasional instance the diagnosis was not only impossible by gross inspection but exceedingly difficult even by microscopic examination. In Case 7 several well-qualified pathologists interpreted the microscopic findings as those of Hodgkin's disease and only after eleven years had elapsed could the issues be decided in favor of pyogenic granuloma. The dura itself was commonly but not invariably thickened adjacent to the epidural lesions. Microscopically the collagenous bundles of this structure were edematous and infiltrated with inflammatory cells. New capillaries and capillary tufts were abundantly in evidence. Some of the larger vessels were occluded by organized thrombi. Punctate abscesses were sometimes observed within the dura itself. In one instance the subdural space immediately underlying the lesion was occupied by a layer of amorphous cellular detritus. The leptomeninges appeared regularly to be implicated by the inflammatory process to a variable degree. In the very mild reactions of the pia-arachnoid the cerebrospinal fluid appeared clear and colorless and often revealed an increased total protein content without pleocytosis. As a later complication the subarachnoid space of the entire cerebrospinal axis was implicated by a bacterial meningitis. More commonly, however, a limited portion of the subarachnoid space corresponding to the epidural lesion was obliterated. Here was demonstrable an outpouring of inflammatory cells and such an organization of mesoblastic elements as to fuse the arachnoid and the pia. The most



significant pathologic findings for the purposes of the present inquiry are those relating to the spinal cord itself. At autopsy the gross appearance of the cord at the level of the lesions was usually normal. However, in some instances the surface vessels seemed unduly prominent. A relative avascularity was disclosed in three specimens. In addition, two specimens showed gross evidence of purulent meningitis disseminated throughout the cerebrospinal fluid spaces. In no case was there a compression deformation of the contour of the spinal cord. By palpation it was usually possible to identify a marked softening of one to several spinal segments at the level of the spinal epidural infection. In three of the cases the softening was so advanced that the removed cord, when folded upon itself, was acutely angulated at the affected level. Gross section of the formalin-fixed cord through the involved region

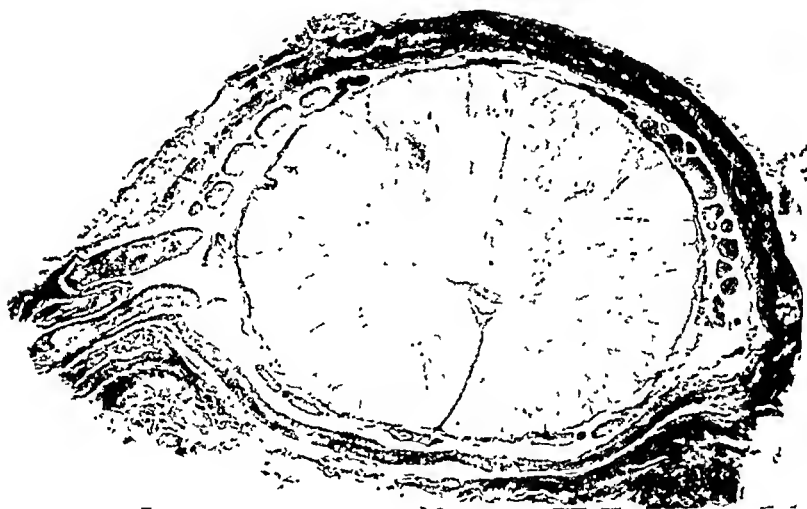


Fig. 1.—Cross section of the cervical spinal cord illustrating the distribution of the areas of status spongiosus.

frequently revealed a loss of architectural features. The gray matter here could not be distinguished from the white. Microscopically the parenchyma of the spinal cord revealed varying changes from specimen to specimen. The most constant finding was that of irregularly scattered areas of status spongiosus (Fig. 1). These areas were in the main peripheral to the ground bundles and did not conform to the topography of the long conduction systems. They were irregular in outline and the finer anatomical alterations consisted of distended spaces, the majority of which were entirely devoid of myelin and axis cylinders, although others contained myelin and axis cylinders in varying degrees of disintegration (Fig. 2). The distribution of these vacuolized zones, particularly in the sections taken from levels not entirely devoid of architecture, was such as to suggest impairment of the intrinsic circulation

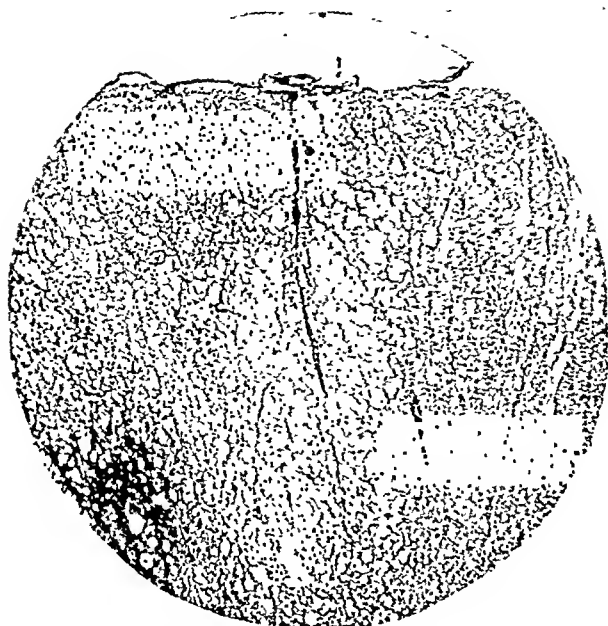


Fig. 2.—Photomicrograph illustrating maximum implication of the parenchymatous elements about an intrinsic blood vessel of the spinal cord. The pattern of the vascularized zone suggests local interference with circulation, although no evidence of thrombosis was demonstrable in this section (Loughlin stain).



Fig. 3.—Photomicrograph illustrating demyelination and loss of axis cylinders about an engorged intrinsic vein of the spinal cord (Weigert stain).

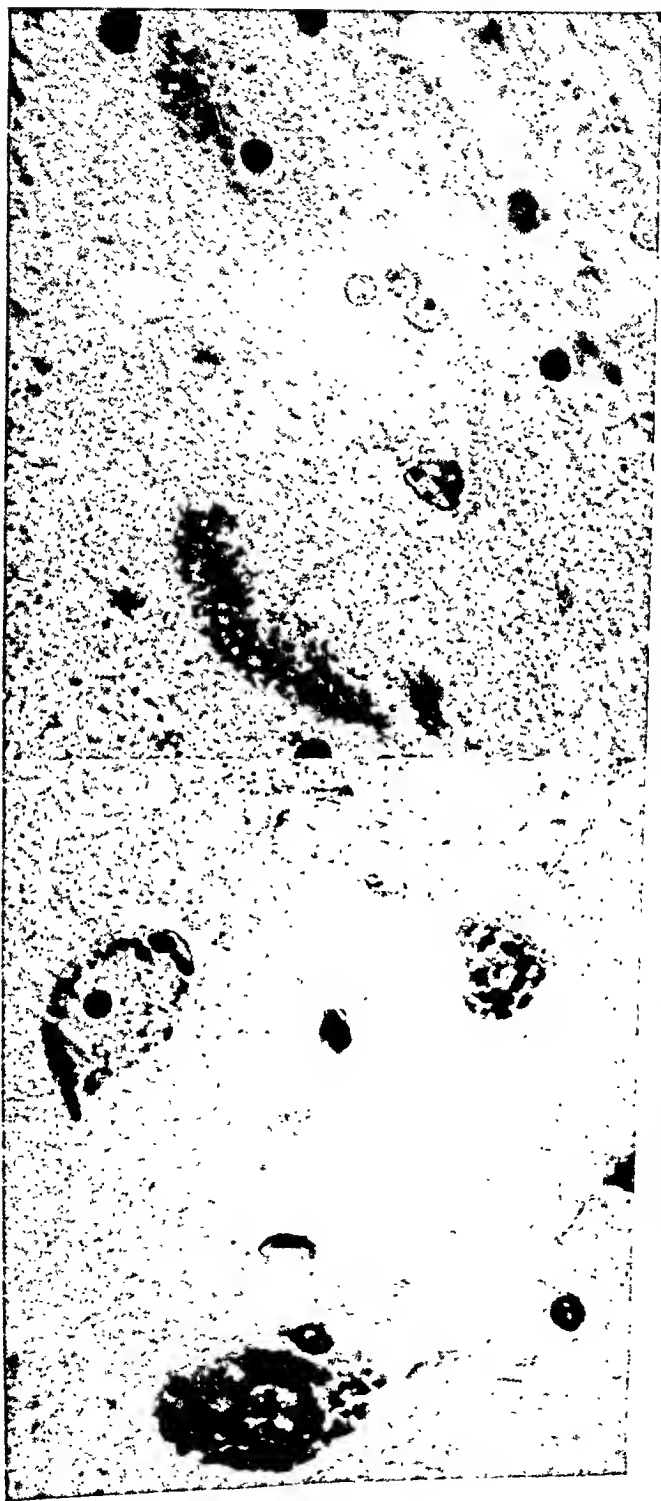


Fig. 1.—Photomicrograph of anterior horn cells. *A*, A less acutely involved segment, showing slight ballooning of neurons without significant changes in the tigroid substance or nuclei (Nissl stain). *B*, A segment of spinal cord underlying an area of epidural infection illustrating loss of cell outline, ballooning, chromatolysis, and early pyknosis. (From Browder and Meyers; *Am. J. Surg.* 37: 1-26, 1937.)

of the spinal cord (Figs. 2 and 3). The glial elements did not appear to be as severely implicated as the neural. The neurons of the gray columns presented all grades of axonal degeneration. According to the degree of involvement at a given level, the anterior horn cells showed changes ranging from early swelling, mild chromatolysis, and eccentricity of the nucleus to disappearance of the cell membrane, complete loss of tigroid substance, and karyorrhexis or pyknosis of the nucleus (Fig. 4). The blood vessels of the pia and spinal cord itself were in some instances found to be thrombosed, but far more commonly they

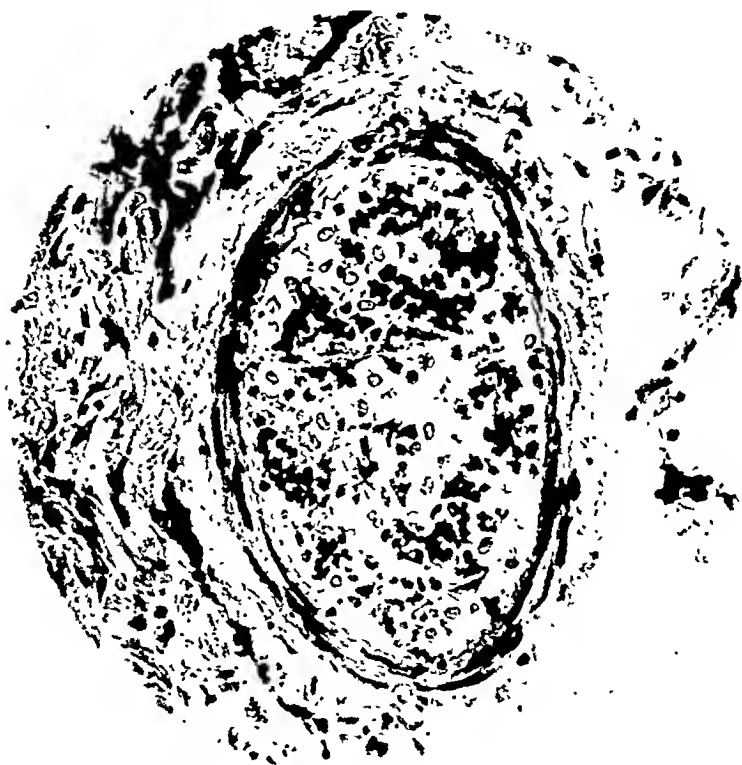


Fig. 5.—Photomicrograph illustrating a thrombosed vessel of the spinal cord in a segment underlying a zone of epidural infection (hematoxylin-eosin stain). (From Browder and Meyers; *Am. J. Surg.* 37: 4-26, 1937.)

were unaltered or at most congested. In one specimen thrombosis of intramedullary vessels was clearly demonstrated (Fig. 5). The specimen obtained from Case 10 with which meningitis was associated was singular in that on gross section a circular area of grayish white tissue occupied the base of the right posterior funiculus over a distance of four lumbosacral segments (Fig. 6). Microscopically this zone was rather sharply demarcated from the surrounding white matter, but its periphery was not marked by a cellular inflammatory response. The internal



B

112. 1—Photomicrograph of anterior horn cells L<sub>5</sub> less acutely involved segment, showing slight ballooning of neurons without significant changes in the thyroid substance or nuclei (Nissl stain). B, A segment of spinal cord underlying an area of epidural infection illustrating loss of cell outline, ballooning, chromatinolysis and early pyknosis (From Browder and Myers Ann J Surg '37 1-26 1937)

responds to the as yet uncomplicated osteomyelitis; radicular pain to the implication of the spinal roots; and, finally, evidence of profound sensory, motor, and vegetative dysfunctions to involvement of the spinal cord itself.

The neurologic signs and symptoms are generally ascribed to the factor of pressure exerted by the epidural lesion against the roots and cord. This interpretation rests for the most part on the clinical demonstration of a block of the spinal subarachnoid space. It appears to be a reasonably defensible deduction in a large number of cases; however, it is inadequate to explain the phenomenon relative to Case 4, in which a complete spinal subarachnoid block was demonstrated when no clinical disability was observable; and that of Case 11, in which the spinal subarachnoid space was entirely patent at a time when a quadriplegia existed. The inadequacy of the pressure factor alone as a complete account of the clinical manifestations is again indicated by our failure to demonstrate at necropsy deformation of the spinal cord at the level of the lesion. Furthermore the mode of recovery following operation, in practically all patients, is strikingly prolonged even though no obstruction to the spinal subarachnoid space is demonstrable. In addition, recovery following drainage of an epidural abscess or the removal of a granuloma is neither as prompt nor as complete as that observed after removal of an epidural neoplasm. These remarks are not intended to deny the existence of a pressure factor in the production of the spinal cord dysfunctions associated with the advanced phases of spinal epidural infections, but rather to deny that pressure is the sole factor. The pathologic demonstration of irreparable parenchymatous changes within the spinal cord is not explicable in terms of pressure alone. Neither can one attribute the intrinsic damage wholly to thrombosis of the vessels of the spinal cord, as have certain authors. After a thorough histologic search such a lesion could be demonstrated in only one of our cases and in this specimen the parenchymatous changes were closely simulated by other specimens in which thrombosis was not discovered. An attempt to explain these observations logically serves to focus attention on the incompleteness of our knowledge concerning the details of the circulation of blood and cerebrospinal fluid within the cord, the manner of fluid exchanges, and the limitations of our present methods for demonstrating many morphologic alterations. The most that may be said at present with respect to these pathologic changes in the spinal cord is that they are the result of circulatory alterations within the cord itself.

As indicated in Table I, ample time for diagnostic consideration usually elapses between the onset of the pain in the back and the early manifestations of spinal cord involvement. It is during this period that a diagnosis of vertebral osteomyelitis may be made and drainage by laminectomy may be instituted before the spinal cord becomes implicated. The practical application of this suggestion has been demon-

structure of this area disclosed broad sheets of mesoblastic cells most resembling those of the pial septa. Contrasted with the relatively uniform dispersion of the axones elsewhere in the section, those in the affected area presented an agglomerated appearance. In none of the specimens were either ectodermal or mesodermal cells encountered within the spinal cord which could be interpreted as those of an inflammatory reaction.

There were three cases in this series with lesions classified as chrome pyogenic granuloma. None of these died; consequently material for the study of the spinal cord in this type of case has not yet been available. An excellent description of the pathologic changes in the spinal cord from a case of epidural granuloma was reported by Hassin in 1928.<sup>5</sup>

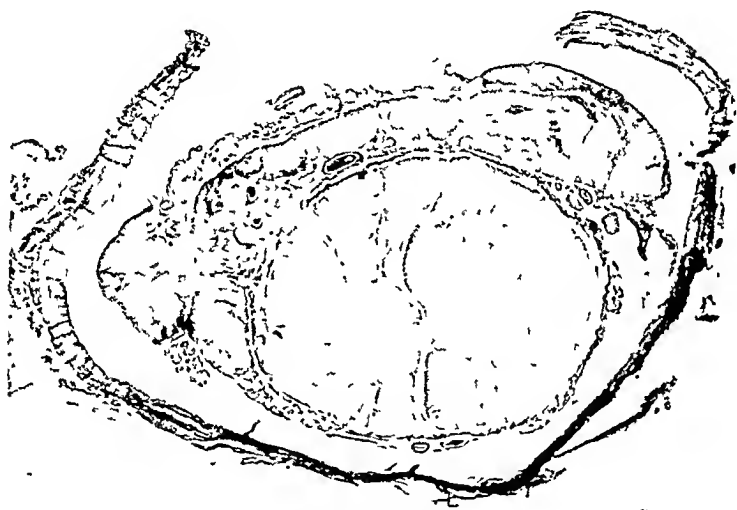


Fig. 6.—Cross section of the spinal cord, illustrating circular zone located at base of right posterior funiculus as described in the text. The severe meningeal reaction in the piaarachnoid is clearly in evidence.

#### DISCUSSION

A critical analysis of the series of fourteen cases under present consideration reaffirms the conviction previously expressed that the vast majority of infections of the spinal epidural space established by metastasis are preceded by vertebral osteomyelitis. With but few exceptions the etiologic agent of this clinical entity is staphylococcus. The sequence of events characterized by a severe, or more commonly by an insignificant, infection associated with or followed by boring pain in the back, radicular pain, and subsequent evidence of spinal cord involvement in this order is practically pathognomonic of this disease. The pathologic lesions that have been described are, in the main, consistent with the clinical features. Thus, the period of boring pain in the back cor-

## RUPTURES OF THE PECTORALIS MAJOR MUSCLE

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**P**ECTORALIS major muscle tears are not common. Including the one presented here, only eighteen cases have been reported, chiefly in French, German, and British literature. Eight cases were reviewed by Gilereest<sup>7</sup> in 1939. Patissier,<sup>14</sup> in 1822, apparently recorded the first case in a butcher boy, the pectoralis major having been torn when the boy attempted to unhook an enormous piece of beef. The patient died of the inflammation which supervened. Letenneur (1862)<sup>9</sup> saw a case in which the pectoralis was torn while the patient was trying to stop a runaway horse. Good function was obtained after immobilization of the shoulder for two weeks. Smart (1873)<sup>19</sup> described a case in a 33-year-old carter who was run over by a van. Rédard (1878)<sup>16</sup> described in detail a case of incomplete rupture of the pectoralis produced by a violent effort to recover balance in a fall from a carriage, whereupon the wheel passed over the strongly contracted muscle. The tear healed by fibrous union. Régeard (1880)<sup>17</sup> diagnosed the condition in a laborer who was thrown out of an upsetting lorry, the left arm being trapped in the wheel. Malinowski (1885)<sup>10</sup> reported a case in a 20-year-old farmer who fell off a horse. There was resultant weakness in the arm, with gradually increasing function. However, the weakness suddenly returned a year later while the patient was doing gymnastics. Tear of the pectoralis major at its attachment to the humerus was diagnosed; operative treatment was recommended but was refused. Weinlechner (1884)<sup>20</sup> saw one case in an infant, consequent upon difficult labor. A case was seen by Knaak (1900)<sup>8</sup> in which the tear of the muscle resulted from a strong pull. Heimann (1908)<sup>6</sup> described two cases, both in exceedingly muscular men, resulting from excessive tension on the contracted pectoralis together with direct powerful blows to the muscle. With various physical therapeutic measures, less than 50 per cent restoration of function was obtained in either case. Coues (1920)<sup>2</sup> published the only report in this country. A 21-year-old boy ruptured the pectoralis while lifting a tackle, when he gave a quick jerk to the rope with his arm held high. Mandl (1925),<sup>11</sup> Eislerberg (1925),<sup>4</sup> and McKelvey (1928)<sup>12</sup> each saw a case where the rupture was produced by a sudden violent pull on the contracted muscle. Mandl's case was not seen until one and one-half years after the accident when some weakness in the limb persisted. In Borchers

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strated by reports of Slaughter, Fremont-Smith, and Munro<sup>9</sup> and of Cohen.<sup>3</sup> It seems that infection of bone may be arrested if not actually cured by chemotherapeutic agents represented by sulfanilamide and its derivatives. These may prove to be a valuable adjunct in the treatment of vertebral osteomyelitis.<sup>10</sup>

#### SUMMARY

The important features of fourteen cases of pyogenic infections of the spinal epidural space have been recorded and the outcome in each instance indicated. The pathologic findings in twelve of the fourteen cases strongly support the opinion that each of these epidural infections was secondary to vertebral osteomyelitis. The gross and histologic studies of the specimens removed at autopsy disclosed changes in the spinal cord which were not wholly ascribable to a pressure factor but which appeared to be the result of stasis. The time interval between the onset of pain in the back and the appearance of neurologic signs is sufficiently long to permit surgical drainage of the infected area to be instituted before the spinal cord becomes irreparably damaged. The use of chemotherapy as a helpful adjunct to the surgical treatment of the disease has been suggested.

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shoulder and over the left side of the chest, and swelling and ecchymosis developed in the region of the anterior axillary fold. The shoulder was painful on attempted motion and the patient kept the arm splinted against the chest wall for comfort. The patient's family physician sent him to the hospital two days later on Jan. 24.

Examination at this time revealed marked ecchymosis and swelling over the entire left pectoral region, especially in the anterior axillary fold. The area was tender to palpation, and a defect about three-quarters to one inch wide could be felt between the two portions of the torn muscle in the region of the anterior axillary fold. Medially the belly of the muscle was easily palpated; the portion on the axillary side of the tear was less discernible. When the patient was asked to adduct the arm, the muscle was felt to move and he complained of pain over it. On forced adduction against pressure, marked weakness was noted in the left shoulder. X-ray examination of the shoulder was negative for evidence of fracture of the clavicle, humerus, and ribs. The clinical diagnosis was incomplete rupture of the left pectoralis major muscle.

At operation on Jan. 25, the swelling was noted to have subsided somewhat after application of cold compresses. Under ether anesthesia a vertical incision was made from the level of the coracoid process downward. The skin and subcutaneous tissues were reflected back and the torn edges of the pectoralis exposed. A blood clot filled the defect between the two muscle fragments, which were separated for a distance of about one inch. The muscle fibers were retracted toward the chest wall. The tear was found to be at the junction of the muscle belly with its tendinous portion. The muscle fragments were reapproximated with difficulty because of the extent of the retraction. The muscle was sutured with white silk sutures and the overlying sheath was also reapproximated with silk. A small Penrose drain was inserted into the lower portion of the wound and the skin closed with silk. The drain was removed two days later, Jan. 27. The patient was discharged on Jan. 29, the wound healing and in excellent condition. He was later seen in the follow-up clinic and gradual restoration of function in the adduction of the left shoulder was noted.

He was seen one year later and claimed that there was complete restoration of function. He was well able to carry on with his occupation (paper hanging) and claimed no loss of strength in the left shoulder. In this period some widening of the skin scar had been noted, probably due to stretching of the part. The scar was not adherent to the underlying tissues. The sutured portion of the muscle was thinner than the remainder of the muscle belly, but there was firm fibrous union of the fragments.

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and Tontscheff's case (1932): partial tear of the pectoralis major was produced by a combination of direct trauma and pull on the contracted muscle.

In contrast it is interesting that Moulouguet (1924)<sup>13</sup> reported sudden spontaneous rupture during cold weather in a 72-year-old man on leaving an overheated room. The hematoma resulting increased enormously and the patient died. There was a past history of injury to the shoulder which had permanently weakened the limb. The tear was attributed to senile changes. Horton (1925)<sup>7</sup> also saw a case in an aged invalid in which there was no history of injury and likewise attributed the rupture to senility.

Saar,<sup>15</sup> Bernhard,<sup>1</sup> and others state that the injury is not uncommon in sports but is infrequently diagnosed.

Rupture of the pectoralis major muscle presents a typical clinical picture. One finds tumefaction and discoloration over the pectoral region with indentation over the rupture site. By having the patient attempt strong adduction against resistance, the separation and the swelling increase, the lump hardens, and the pressure over it causes pain. The force with which adduction is accomplished is directly in relation to the degree of the tear. When the contraction ceases, the lump becomes soft again. Attempted motion is usually accompanied by pain over the torn muscle.

Tears of the pectoralis may develop either by (1) excessive muscle tension, (2) direct violence, or (3) a combination of both. Two cases have been reported as spontaneous ruptures due to senile changes. Pirker<sup>15</sup> believes old age is a predisposing factor. Of the other cases nine were attributed to strong pull on the contracted muscle, one to direct violence, and five to a combination of both direct blows and violent pull. All cases occurred in males. The tears involved the muscular portion in every case, usually the pars sternalis and the pars abdominalis, near the axillary fold. Tears of the clavicular portion and of the part attached to the sternum are less frequent. Complete tears have never been reported.

As regards treatment, surgical repair of the muscle through suture is preferable if seen early, and plastic operation is advisable in cases where the diagnosis has been delayed. There is a normal tendency for spontaneous restoration of function, but this is slow and full power is never restored.

CASE REPORT.—F. L. S. (F. H. No 3576 G), aged 67 years, an American white male paper hanger, was admitted on Jan. 24, 1938, and discharged on Jan. 29, 1938. This patient stumbled and fell down the cellar stairs in his home on Jan. 22, 1938. About one half the way down the stairs there was a railing which he reached out for with the left hand to try to check his fall. There was a strong forcible adduction in the abducted position of the outstretched left arm. The patient thought he felt something "give" in the left shoulder. There was immediate pain in the left

## DUPUYTREN'S CONTRACTURE

### OPERATIVE CORRECTION BY USE OF TUNNEL SKIN GRAFT

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SUCH a condition has been the subject of operation for more than a century. As the name implies, it was first described by Dupuytren in 1832 as resulting from contraction of the palmar fascia. Even before this various operative procedures were being done for the deformity. An American edition of Fergusson's<sup>1</sup> *Surgical Practice*, published in 1845, described the condition under the chapter entitled "Incisions and Excisions," showing drawings of the hand with the little and ring fingers in a state of permanent contraction. The affection was described as showing itself by slight inability to extend one of the fingers (generally the little one) which, at last, in the progress of years, worked up into the palm. By this time the ring finger also would have assumed a nearly similar state, and possibly too, the middle finger would be somewhat rigid. During this period it was the opinion of dissectors that the cellular tissue between the skin and palmar aponeurosis was the cause and not contraction of the flexor tendons. It appeared to observers at this time, when the contracture was extreme, that the skin, cellular tissue, fascia, and even tendons were in a more or less state of permanent rigidity. They also believed that one or another of the structures might be more in fault than the rest. It was also noted that the lumbricales and interossei muscles might play a part in certain cases. This observation was rather interesting, since recently Kaplan<sup>2</sup> has shown that the condition was probably due to the contracture of the phalangeal insertion of the pretendinous bands of the palmar aponeurosis and had little or nothing to do with the deep extension of the palmar aponeurosis toward the deep interossei fascia. He suspected that cases which did not have digital prolongations would not develop Dupuytren's contracture.

It is often stated that those who are so employed as to cause much pressure on the palm of the hand, such as gardeners, carpenters, etc., are more subject to this condition than others. The evaluation of this statement is rather difficult since the frequency of its occurrence in those doing little manual labor, such as clergymen, physicians, bankers, etc., in some series of cases reported is greater. However it is noted that the contracture in these patients came on after middle age and they gave a history of doing considerable strenuous labor in early life. Some writers feel that Dupuytren's contracture occurs more commonly in females

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than is ordinarily considered, but that the disease is overlooked because it is less severe. The disease has not been seen in the colored race. The right hand is most commonly affected. In bilateral cases the involvement of the left hand may precede the right by several years or may occur simultaneously.

The etiology is still obscure. There are many theories, it being quite possible that the primary cause is not always the same though the end result is. Trauma of varying severity has been recorded in case reports, also low-grade local inflammatory process and chronic dental infection. Two predisposing factors have been mentioned: the loss of the protective layer of subcutaneous fat associated with advancing age and the fact that the little and ring fingers are used more than the others in the act of grasping and are flexed more tightly as the hand is closed. The latter, on first thought, appears farfetched, but this is what actually happens in grasping a golf club. A second possible cause is a constitutional tendency to gout or rheumatism. This theory has many adherents. A third possible factor is heredity, occasionally noted in cases reported. This cannot be denied and apparently can be transmitted from either the maternal or paternal character. A further possible cause is disturbance in calcium metabolism. Cases are reported which were hypocalcemic and improved with parathyroid extract. We know of the relation of hypercalcemia with scleroderma affecting the connective and elastic tissue. For this reason we should bear in mind a disturbed function of the parathyroids.

The pathology is essentially a hypertrophy and continuation of the fascia of the hand. The disease usually begins as an isolated nodule in the fascia over the flexor tendon of the ring finger. Other nodules may appear in line with the first or over the flexor tendon of the little finger. A small dimple develops just distal to the primary nodule, drawing the skin up in a crescentic fold. The middle and index fingers may also become involved. The disease is usually progressive, but it may be a few months to ten to fifteen years before the finger is contracted on the palm. During this time the overlying skin becomes calloused. It loses all its normal characteristics and becomes so intimately connected with the fascia in some cases that it is impossible to separate them at some points. The digital blood vessels and nerves may be compressed or displaced from their normal position.

According to the early textbooks on surgery, subcutaneous division of the rigid textures was practiced. This was followed by gradual extension of the fingers on a splint. Apparently that apparatus was constructed to fit the peculiarities of the case and the ingenuity of the surgeon went far to obviate and remove the deformity. The present treatment consists of complete excision of the contracted fascia. If the viability of the skin is in doubt, it is excised and the defect is filled in with a free, full-thickness graft. Pedunculated grafts have been used but

offer no better results besides being too time-consuming and causing more discomfort for the patient. In early cases radium has been advocated by Feurstein.<sup>7</sup> He feels that it is the choice treatment, although it does not give a perfect cosmetic result.

In selected cases I have been using full-thickness, tunnel skin grafts to fill in the defect. This type of graft was developed by Keller<sup>8</sup> for various postwar defects. The mechanical principles that form the basis for success in grafting work very well for this type of graft in Dupuytren's contraction. Accurate coaptation of the graft is obtained throughout the area to be epithelized; firm pressure and tension are also maintained over the area. This avoids excessive secretion and venous stasis.

#### TUNNEL SKIN GRAFTS IN DUPUYTREN'S CONTRACTURE

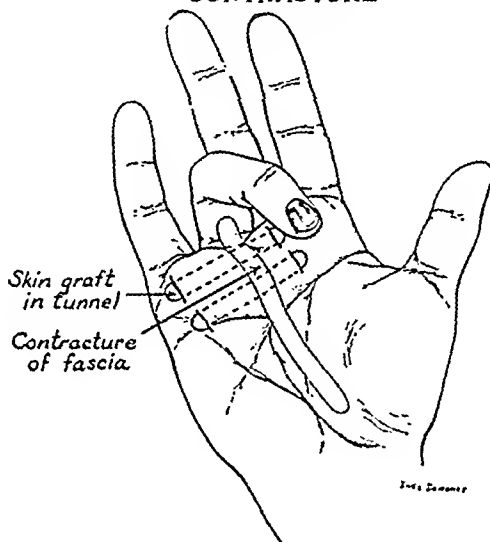


Fig. 1.—Tunnel skin grafts in Dupuytren's contracture.

The operation is performed under gas anesthesia, using a blood pressure cuff as a tourniquet. An incision is made along the ulnar surface of the hand curved slightly inward at its proximal end. This exposes the narrow upper end of the fascia which is isolated, clamped, and cut. The fascia can then be lifted upward and away from the palm by gentle traction on the forceps, allowing division of the numerous fasciculi as they pass in different directions. The separation of the skin from the fascia, especially at the point of the nodules and pitlike depressions, is rather difficult. Careful dissection is necessary or one may buttonhole the skin. The dissection is carried distally until all contracted fascia has been removed. If the contracted fascia extends into the phalanges, which it usually does, separate incision and dissection may be necessary. In doing this care is taken not to injure the digital nerves and vessels. This dissection, along with freeing of the skin, is the most difficult part

than is ordinarily considered, but that the disease is overlooked because it is less severe. The disease has not been seen in the colored race. The right hand is most commonly affected. In bilateral cases the involvement of the left hand may precede the right by several years or may occur simultaneously.

The etiology is still obscure. There are many theories, it being quite possible that the primary cause is not always the same though the end result is. Trauma of varying severity has been recorded in case reports, also low-grade local inflammatory process and chronic dental infection. Two predisposing factors have been mentioned: the loss of the protective layer of subcutaneous fat associated with advancing age and the fact that the little and ring fingers are used more than the others in the act of grasping and are flexed more tightly as the hand is closed. The latter, on first thought, appears farfetched, but this is what actually happens in grasping a golf club. A second possible cause is a constitutional tendency to gout or rheumatism. This theory has many adherents. A third possible factor is heredity, occasionally noted in cases reported. This cannot be denied and apparently can be transmitted from either the maternal or paternal character. A further possible cause is disturbance in calcium metabolism. Cases are reported which were hypocalcemic and improved with parathyroid extract. We know of the relation of hypercalcemia with scleroderma affecting the connective and elastic tissue. For this reason we should bear in mind a disturbed function of the parathyroids.

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#### TUNNEL SKIN GRAFTS IN DUPUYTREN'S CONTRACTURE

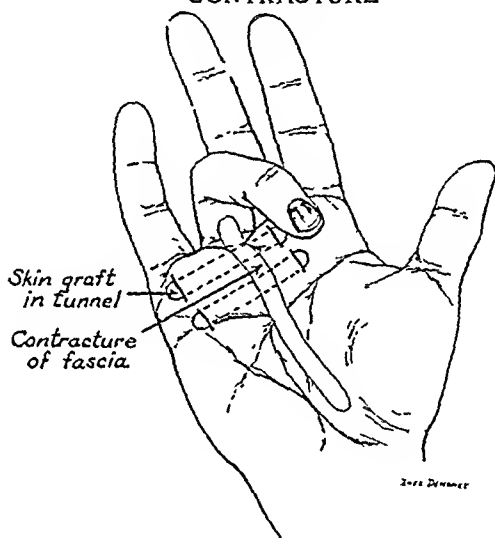


Fig 1.—Tunnel skin grafts in Dupuytren's contracture.

The operation is performed under gas anesthesia, using a blood pressure cuff as a tourniquet. An incision is made along the ulnar surface of the hand curved slightly inward at its proximal end. This exposes the narrow upper end of the fascia which is isolated, clamped, and cut. The fascia can then be lifted upward and away from the palm by gentle traction on the forceps, allowing division of the numerous fasciculi as they pass in different directions. The separation of the skin from the fascia, especially at the point of the nodules and pitlike depressions, is rather difficult. Careful dissection is necessary or one may buttonhole the skin. The dissection is carried distally until all contracted fascia has been removed. If the contracted fascia extends into the phalanges, which it usually does, separate incision and dissection may be necessary. In doing this care is taken not to injure the digital nerves and vessels. This dissection, along with freeing of the skin, is the most difficult part

of the operation. After controlling all hemorrhage, the skin is obtained for the tunnel graft. Two or three grafts are put in place transversely under the skin depending upon requirements of the case. The grafts are placed under the areas of devitalized skin, this also determining the width of the graft. The source of the graft is unimportant except that due consideration should be given to the location as to texture and hairlessness. The skin of the area from which the graft is to be taken is prepared the day before operation along with the hand. The graft is

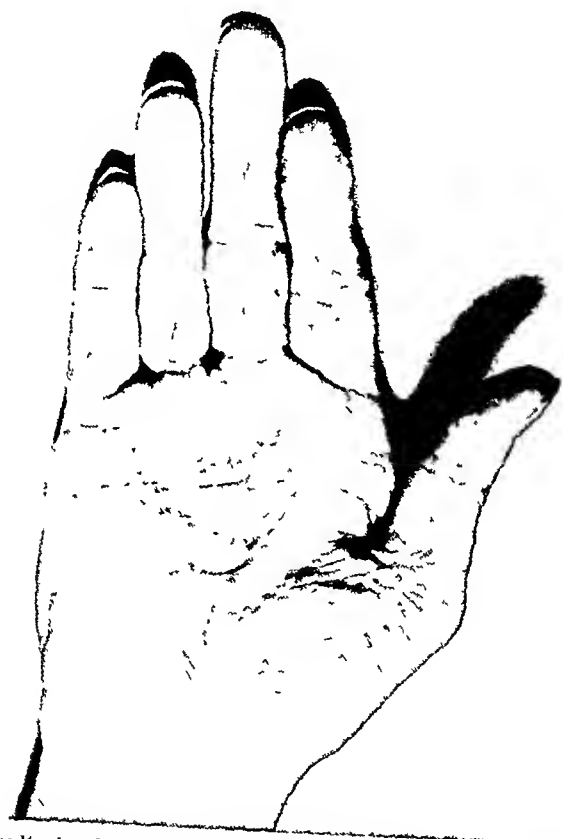


Fig. 2—End result showing grafts in palm of hand and complete extension of the fingers

outlined on the skin of a size estimated to be necessary, then carefully and gently dissected free with a sharp knife as fat free as possible. Small puncture wounds are then made at necessary points opposite the incision followed by simply placing the tunnel graft with the raw surface downward, pulling one end through the puncture wound on one side and letting it extend beyond the incision on the other side. (Fig. 1.) The wound is then sutured snugly with fine silk and without drainage. It is not necessary to suture the ends of the grafts in place. Five

or six layers of vaseline gauze are then placed over the palm of the hand before applying the dressing. The dressing is held in place with a tight bandage, the forearm and hand being splinted with the finger in extension. The bandage is tightened on the fourth or fifth day and is not removed until the tenth or fourteenth day. At this time, under local anesthesia, the skin is cut over the grafts and a portion removed if necessary; however, usually the edges are allowed to retract or atrophy. Twenty per cent argyrol dressing is applied for a few days followed by whirlpool, massage of the fingers, and exercise. At this stage cod liver oil ointment is a satisfactory dressing with splinting of the fingers in extension at night.

The use of this type of graft in this affection offers several advantages. I have used this graft for various other conditions and its growth has been more universally successful than any other type. The vitality of the graft seems greater; it is completely surrounded by living tissue which furnishes an ideal environment, and, if it is necessary at any time to change the dressing, it will not disturb the graft. By using it in this manner, close apposition is assumed, movement does not occur, and accurate fitting and cutting are unnecessary. The maintenance of proper tension is no problem and mild infection does not affect the graft. The graft is capable of adjusting itself to a movable contour of the underlying parts. The whole procedure is quicker, less tedious, not uncomfortable to the patient, and gives the surgeon less anxiety.

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# FURTHER OBSERVATIONS ON THE ETIOLOGY OF VASOMOTOR DISTURBANCES FOLLOWING PERIPHERAL NERVE SECTION

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(From the Peripheral Vascular Clinic, Department of Surgery, Cleveland City Hospital, and the School of Medicine, Western Reserve University)

IN A PREVIOUS communication<sup>1</sup> evidence was presented indicating that the frequently observed nutritional changes which develop in digits that have been deprived of their peripheral nervous innervation may be initiated by a vasospasm having its origin in the well-known phenomenon of "adrenaline sensitization."<sup>2-8</sup> It has been repeatedly demonstrated that arterioles which have lost their postganglionic sympathetic innervation do become abnormally sensitive to minute quantities of circulating adrenaline. Since the postganglionic vasomotor fibers reach the blood vessels of the hands and feet via the branches of the brachial and lumbosacral plexuses respectively,<sup>9-11</sup> such sensitization should follow their division. The aforementioned report was based on a controlled experiment performed in an individual who had suffered a traumatic division of the median and ulnar nerves at the wrist. Following the subcutaneous injection of 0.35 c.c. of 1 per cent neosynephrin hydrochloride, a conspicuous decrease in the skin temperatures of the anesthetic digits ensued, the surface temperatures of the opposite hand remaining unaffected. More recently precisely similar findings have been reported by other investigators.<sup>12</sup>

The following is a case of peripheral vasospasm following the surgical section of a median nerve. It presents several unusual features which merit reporting.

## CASE REPORT

H. L. (No. 211840) was admitted to Surgical Service A at Cleveland City Hospital Aug. 17, 1939, with the following complaint: For the past year a tumor on the inner side of his right arm had been steadily increasing in size. The slightest movement of or pressure on the tumor produced shocklike paresthesia in the second and third fingers.

Examination showed a white male, aged 22 years. Situated in the medial portion of the right arm was a firm mass measuring approximately 4 by 3 cm. It appeared to be firmly attached to the deeper structures and was slightly tender. Manipulation produced paresthesia in the distribution of the median nerve.

The mass was explored. An ovoid growth measuring 4 by 2 cm. was exposed. It involved the median nerve. Local extirpation appeared impossible, and so the tumor together with 1½ inches of adjacent nerve trunk were excised. The pathologist made a microscopic diagnosis of neurofibroma with questionable malignant change. The operation was immediately followed by paralysis and anesthesia of the structures in the hand innervated by the divided median nerve.

About ten days following neurectomy, the patient began to experience aching pain in the anesthetic portion of his hand. The pain became increasingly severe and soon reached the point where he could not sleep. I saw the patient fifteen days after the operation. The pain had certain definite characteristics. It was not cutaneous but was deeply situated in apparently anesthetic tissue; it was aching but not burning; it was constantly present; it was limited to the volar aspects of the first three fingers and the adjacent portion of the palm and did not radiate or shoot; and it could be partially relieved by prolonged application of heat to the painful part.

Objectively, the portion of the hand innervated by the sectioned median nerve was dry, cold to the touch, and deeply cyanotic (Fig. 1). Cutaneous sensibility in this area was absent. The remaining portion of the hand was cooler than normal and was covered with perspiration. There was total paralysis of the muscles in the hand and forearm innervated by the median nerve. The operative wound was clean.

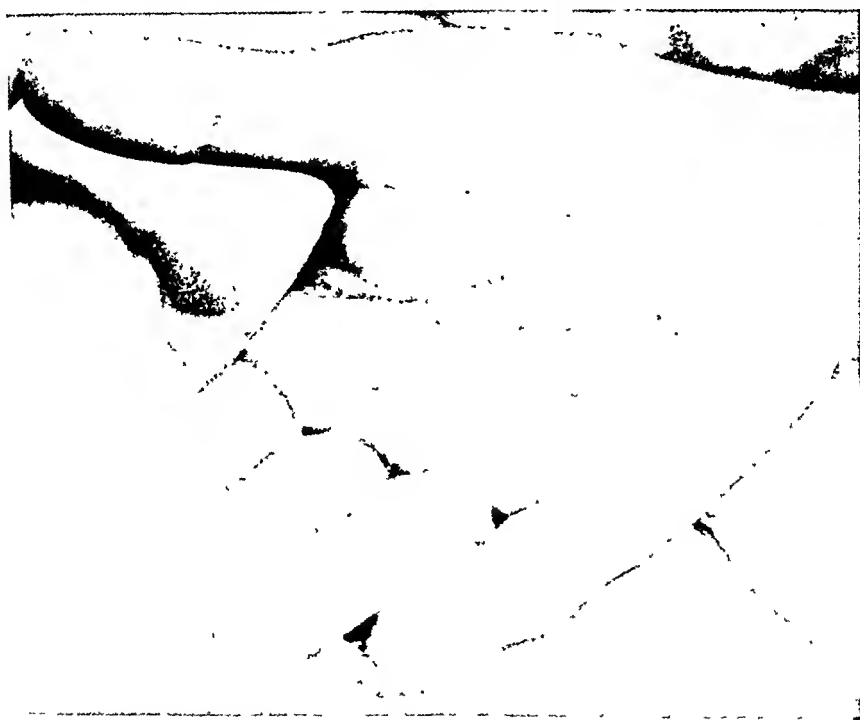


Fig. 1.—The triangular-shaped patch of cyanosis outlining the zone of the peripheral cutaneous distribution of the median nerve in the hand.

This case presented a threefold problem: (1) of explaining the presence of pain in apparently anesthetic tissue; (2) of determining how the painful impulses reached the central nervous system; and (3) of determining what to do to relieve the pain. The nature of the pain suggested that it had its origin within the tissues of the hand as a result of the observed vasospasm. To determine whether this vasospasm was related to the phenomenon of "adrenaline sensitization," 0.5 c.c. of 1 per cent neosynephrin hydrochloride was injected subcutaneously. No decrease in skin temperatures followed, for the reason that superficial vasoconstriction was so intense that a further decrease in surface temperature could not occur. However, within a few minutes of the injection, the deep-seated pain increased in severity to the point where morphine had to be administered.

On the following day the ulnar nerve was blocked with procaine at the region of the elbow. (Leiche<sup>13</sup> had reported connections between the ulnar and median nerves in the palm. He describes an instance where traction on the surgically exposed ulnar nerve produced pain in the distribution of the median nerve in the hand.)

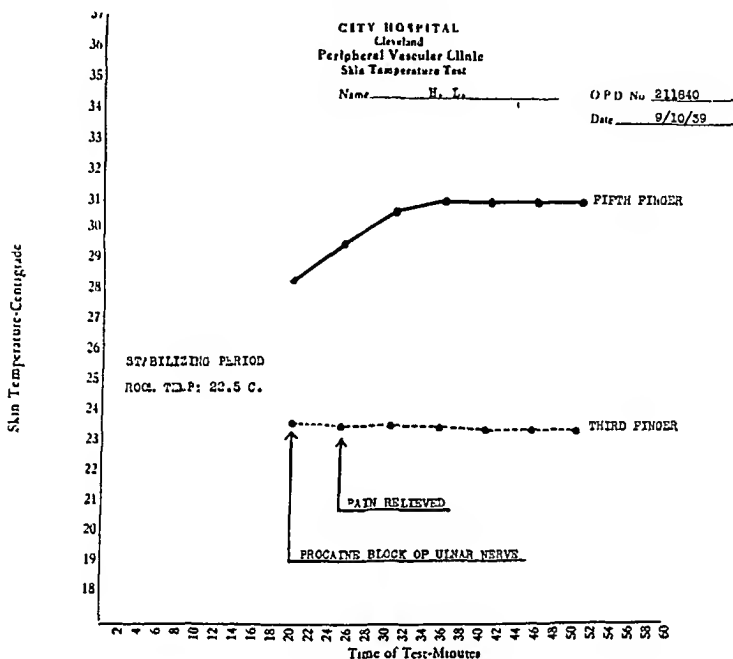


Fig. 2.

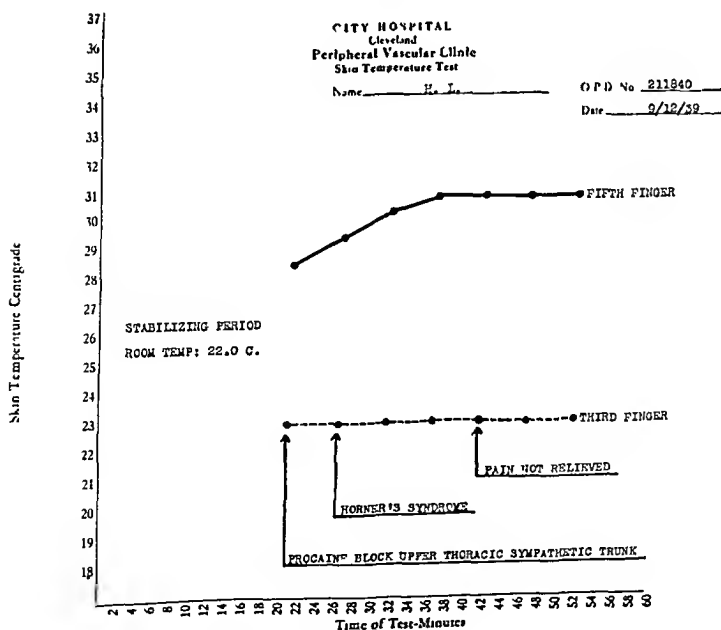


Fig. 3.

Anesthetization of the ulnar nerve was followed by immediate, complete relief of pain which lasted for several hours. The skin innervated by the blocked ulnar nerve became hot and dry. The surface temperatures of the portion of the hand innervated by the sectioned median nerve and in which pain was felt remained constant (Fig. 2). On a subsequent day the ulnar nerve block was repeated with similar results.

It was evident that pain production was in the hand and that painful impulses were being carried over the ulnar nerve. It remained to be determined whether the afferent fibers carrying these sensations were somatic or sympathetic. Accordingly, a procaine block of the upper portion of the right thoracic sympathetic trunk was performed. A Horner's syndrome followed. Skin temperatures in the ulnar distribution rose to maximum vasodilatation levels, while those in the median nerve distribution remained constant (Fig. 3). Pain was not affected.

A final diagnosis was made of severe vasospasm in the peripheral distribution of a divided median nerve with irritation of extravascular somatic sensory nerve fibers, the fibers reaching the ulnar nerve through anastomotic connections between it and the distal portion of the divided median nerve.

Despite the negative results obtained with a procaine block of the sympathetic trunk, it was deemed advisable to perform a sympathectomy in order to abolish the reflex vasomotor disturbances which were beginning to affect the innervated portion of the hand. In addition, it was hoped that the resultant increase in temperature of the tissues surrounding the painful region by contiguity would progressively relax the spastic vessels in that region.

Following the sympathectomy the entire right hand was dry, and with the exception of the portion innervated by the sectioned median nerve, it was pink and warm. Within a few days the patient began to experience some diminution in the intensity of the pain in the palm. Two weeks later the pain had completely disappeared in the palm, but it was still present unabated in the fingers. Two months later the pain had disappeared from all but the tips of the anesthetic fingers. Six months later there was no pain, cyanosis in the anesthetic skin had disappeared, and its surface temperature had risen an average of  $4^{\circ}$  C. Ten months following the initial operation tests were performed to determine whether "adrenaline sensitivity" in the peripheral distribution of the destroyed median nerve still remained. Five-tenths cubic centimeter of adrenaline was injected subcutaneously, and readings of the surface temperatures of the second, third, and fifth fingers were taken. The results obtained are shown in Table I. It will be observed that, while the skin temperatures in the fifth finger remained constant, those in the anesthetic second and third fingers conspicuously decreased.

#### COMMENT

There is little further to say concerning the mechanism of pain and vasospasm production. However, this case does present another point requiring emphasis. It has been recently suggested<sup>12</sup> that the phenomenon of "adrenaline sensitization" tends to disappear in a few months, and that there is no particular advantage accruing to the preganglionic types of sympathectomy. The observations in the reported case are at variance with these suggestions. The type of sympathectomy performed in this instance was preponderantly preganglionic. It consisted of the excision of the second thoracic ganglion through a posterior approach.<sup>14</sup> As a result we were dealing with a somewhat unique situation in which a surgical division of postganglionic fibers innervating the blood vessels of one portion of a hand was immediately followed

TABLE I

REACTION OF SURFACE TEMPERATURES OF SECOND, THIRD, AND FIFTH FINGERS TO SUBCUTANEOUS INJECTION OF 0.5 G.C. 1:1,000 ADRENALINE\*

	FINGERS		
	SECOND	THIRD	FIFTH
Resting skin temperature	28.9°	28.9°	31.9°
Room temperature, 24.5° C.			
5 min. after injections	28.0°	28.0°	32.0°
10 min. after injections	27.5°	27.6°	32.0°
15 min. after injections	27.2°	27.4°	31.9°
20 min. after injections	26.8°	26.8°	31.8°
25 min. after injections	26.7°	26.7°	31.8°
30 min. after injections	26.6°	26.6°	31.9°

\*Test performed ten months after destruction of postganglionic vasomotor fibers to second and third fingers and preganglionic vasomotor fibers to fifth finger.

by a surgical interruption of the preganglionic fibers innervating the blood vessels of the remaining portion of the hand. Table I illustrates that ten months following these operations, the skin temperatures in the region of the preganglionic denervation were distinctly higher than those in the region of the postganglionic denervation, and that while the former remained constant following an injection of adrenaline, the latter conspicuously decreased.

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## AN APPARATUS FOR THE PREVENTION OF POSTOPERATIVE CIRCULATORY STAGNATION

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*(From the Thomas-Davis Clinic)*

IT IS generally agreed that one of the greatest predisposing causes of postoperative embolism and phlebitis is a retardation of the venous blood flow. This stagnation of the circulation is due chiefly to two factors: lessening of the excursions of the diaphragm, thus diminishing the negative intrathoracic pressure; and lack of muscular contractions and tone which pump the venous blood to the right heart. Ample evidence has been presented to prove that the incidence of these postoperative complications can be greatly lessened by means of muscular exercises which accelerate the circulation.<sup>1-4</sup> Wilson<sup>5</sup> and Pool<sup>6</sup> advocated flexing and moving the extremities. Payr<sup>7</sup> attached a roller at the foot of the bed on which the patient made walking movements. Gamble uses a device consisting of two bicycle pedals mounted on a broad base for exercising the lower limbs by pedaling and de Takats and Jesser have recently recommended a similar apparatus. We have devised an inexpensive device using the same principle. It consists of a frame which loops over the end of a bed and pedals which are mounted on a support extended from the frame (Fig. 1). The instrument is easily portable by using the coaster on its base (Fig. 2); there is no possibility of the apparatus slipping and suddenly throwing an unexpected strain on the patient; the heel plates attached to the pedals give support to the legs so that there is no tension on the abdominal muscles, thus protecting fresh abdominal wounds and maintaining muscular strength. Patients who have had previous surgery verify this.

Experience has shown that it is advisable to have a nurse or orderly present while the patient is exercising. For this reason, a foot brace is used to hold the frame firmly against the bed, instead of applying a brace to attach the base to the bed (Figs. 1 and 3). This also simplifies the removal of the apparatus from the bed. To prevent scratching the beds, the inner side of the frame is lined with sponge rubber. Increased resistance to muscular effort is made possible by tightening the bolts at the top of the uprights. More resistance should be added as the patient progresses. All of our postoperative patients, except infants, have used this routinely, and there have been no complaints of pain, fatigue, or discomfort from its use. Not only is the stagnation of blood overcome, but the patient is aided psychologically by giving him something to do to aid in his recovery. The exercises are given three times daily for five to ten minutes, beginning the first postoperative day.



FIG. 1.



FIG. 2.

Fig. 1.—Apparatus in place over end of bed. Orderly's foot on foot brace, giving firm stabilization. Note the heel plates attached to the pedals which give the feet support allowing relaxation of the abdominal muscles.

Fig. 2.—Method of transporting the apparatus from bed to bed. Its weight is approximately 12 pounds.

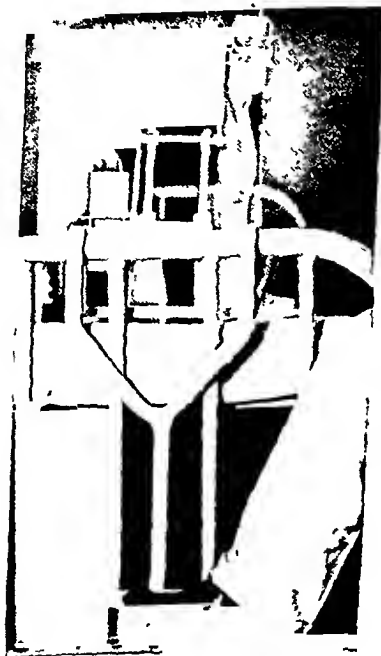


Fig. 3.—Anterior view of apparatus. Bolts at top of upright bars may be tightened to increase resistance to muscular effort

Mr. Ely Wright, engineer at the Southern Pacific Sanatorium, designed and constructed the apparatus under our direction and deserves credit for most of the innovations used.

The equipment used in the construction of this apparatus cost \$3.50. The uprights holding the pedals are automobile connecting rods. Similar apparatus may be constructed by using the accompanying illustrations as a model.

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## CATGUT AND COLLAGEN

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NAGEOTTE<sup>1</sup> has shown that tendon reduced to a collagenous substance by fixation with alcohol or formalin does not behave like a foreign body when implanted into living tissues. Without phagocytic reaction it remains and becomes a part of the connective tissue of the host, subsequently being entered by fibroblasts and becoming a living part of the organism. The implant may be used to replace or repair fascia, tendons, or other tissues. The species specificity of this material is lost by fixation and it, therefore, may be used as a heteroplastic implant.

The significance of this phenomenon of Nageotte can hardly be overestimated, for it offers a new simple source of nonspecific material for plastic surgery or for use as tampons or ligatures. The use of this material for sutures may revolutionize surgical suture technique.

In the recent past ligature materials have been discussed too little. One would judge from the present teaching of general surgery that our suture materials leave nothing to be desired, particularly with the introduction of modern catgut. Our texts mention only two fundamentally different kinds of suture material: the absorbable and the nonabsorbable. Nonabsorbable sutures, such as silk and metal, are easily sterilized and handled, but in the organism they act as foreign bodies and sometimes interfere with wound healing. Absorbable sutures, on the other hand, have caused trouble in the past because of difficulties in sterilization. Catgut, the commonest absorbable suture, is derived from the intestine of cattle, where the most resistant pathogenic bacteria are to be found. Nonresistance to boiling, therefore, has made sterilization the chief problem in the use of catgut, a problem which now has been largely overcome, so that catgut, which was used only in unsterile procedures twenty years ago, is now so generally satisfactory in surgical practice that its shortcomings have been greatly overlooked.

It has been shown that catgut strands in the tissues are quickly invaded by leucocytes and a serous exudate, which so quickly cause swelling and loss of tensile strength in the sutures that they become unreliable within a few days. Such considerations have caused many surgeons to reinforce gastrointestinal suture lines with silk and to lack faith in catgut for herniorrhaphies and plastic procedures.

It was in herniorrhaphies and plastic procedures, as far as I know, that connective tissue from fascial bands, kangaroo tendons, etc., was first used as suture material. In using these suture materials, which

must be considered as antoplastic or heteroplastic transplants, attention was drawn to the nearly forgotten fact that, in the last analysis, the problem of all sutures is one of implantation. The question of the suitability of such material, therefore, cannot be answered by the surgeon alone, for at operation he tests only tensile strength, tying ease, etc. It is seldom realized that extensive experimental work is required to determine the effect of the tissues and the passage of time on the implant.

While the absorbability of catgut is generally recognized, few of us appreciate how long a time or what conditions are required. We know that catgut loosens in fourteen days and assume that this is also the time required for absorption. Von Haefen<sup>2</sup> has recently called attention to the slow and irregular rate of absorption of catgut and I have found segments of catgut scarcely changed in rabbit livers after 216 days. Similar experiments have shown the impossibility of prediction of catgut absorption rates. Various factors affect the rate of absorption, such as the brand of catgut, probably owing to the chemicals used in preparation (chromic acid, iodine, formalin, etc.). The vascularity of the tissue and the degree of tissue damage by the suture also play a role, and necrosis, due to pressure or to the chemicals in the suture, may prevent absorption altogether. In general, all catgut is difficult to find in most tissues after three months or in the peritoneum after six to ten weeks.

Absorption of catgut seems to depend largely on imbibition of serous fluid by the suture material. Leucocytic invasion also occurs and absorption is effected by digestion and phagocytosis. In case the imbibition of fluid is slight, leucocytic action is limited to the periphery of the strands and absorption proceeds much more slowly. Catgut has an affinity for leucocytes by means of which most strands are converted within a few weeks into tubular or band-shaped abscesses. Whether this affinity for leucocytes is a property of catgut itself or the result of the processes by which it is manufactured commercially from the smooth muscle of the gut, I cannot say. In comparative studies iodine-impregnated strands showed a greater affinity for leucocytes than American manufactured chromic catgut. This quality of catgut causes edema as well as leucocytic infiltration in the tissue immediately surrounding the sutures. The assumption that catgut, being an organic substance, is accepted by the tissues without important reaction is therefore entirely wrong.

The irritation of the surrounding tissues by catgut appears to be greater than that caused by nonabsorbable sutures, such as silk. If the claim is made in advertising literature of a modern catgut preparation (Braun) that absorption occurs without reaction, we must consider it a *contradictio in adjecto*. "Healing in" is the reverse of absorption and absorption is the result of the reaction by the tissues; therefore, the result of the irritation of these tissues, which cannot proceed "without re-

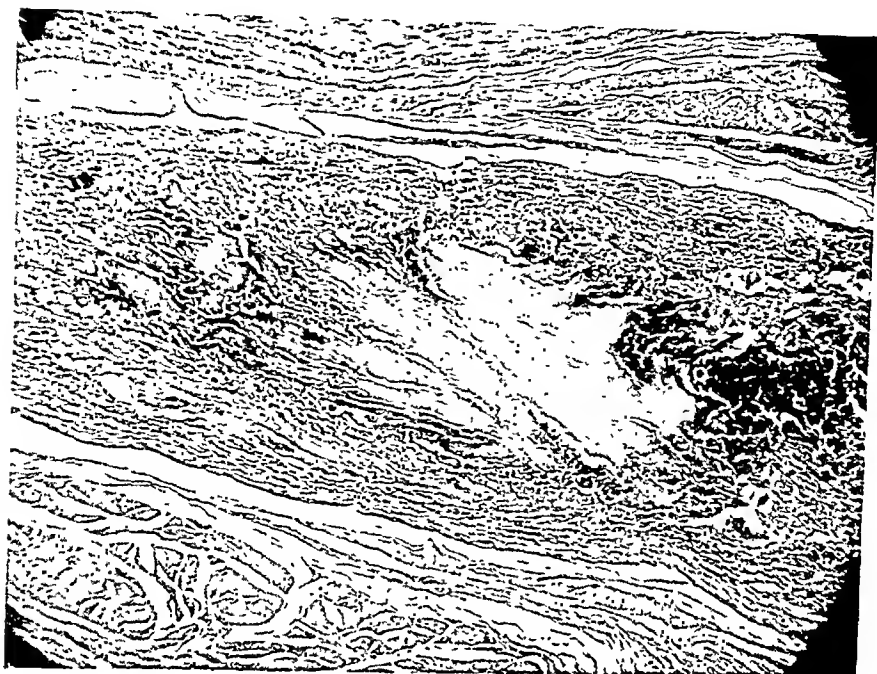


Fig. 1.—No. 1 catgut in the abdominal wall of a rabbit, 107 days after implantation. Peripheral absorption by leucocytes which can be seen invading the frayed material.



Fig. 2.—No. 1 catgut in the liver of a rabbit, 216 days after implantation. The sutures are for the most part unabsorbed. They are surrounded by a layer of leucocytes and a thicker one of connective tissue. A precipitate of calcium salts (dark colored) may be seen on the periphery of the sutures in some places.

action." Catgut, as it is used today, is not a material acceptable by the tissues without reaction but is really a foreign body. The fact that it is not extruded ordinarily, but is destroyed or encapsulated, does not alter the case. These findings discredit one of the principal arguments for catgut and it, therefore, becomes necessary to seek other suture materials homogeneous with the tissues.

Three years ago Van Os and Michaël<sup>3</sup> described a new process by means of which threads were obtained from connective tissue; viz., the suture material brocafil. In the course of my experiments with this substance, and as a result of the technical and histological data obtained

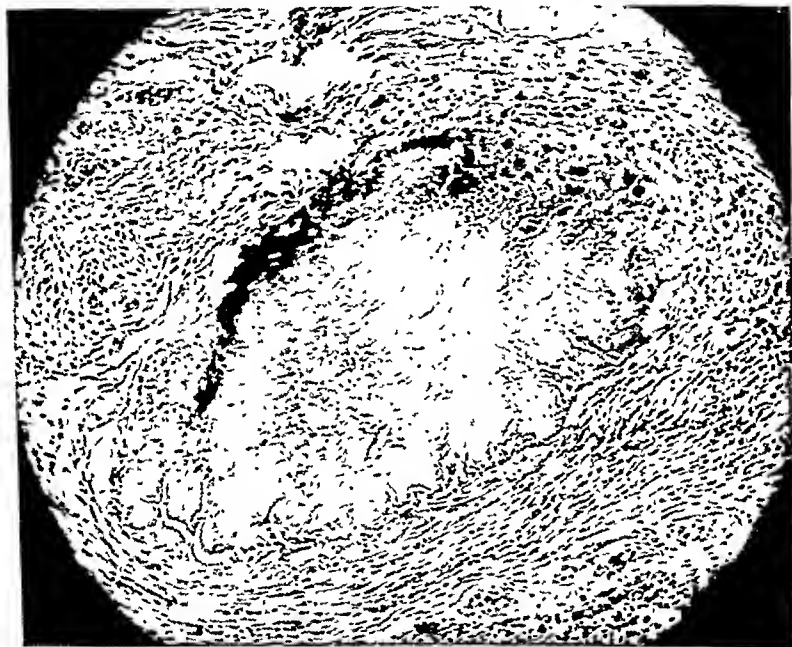


Fig. 3.—No. 1 catgut in the liver of a rabbit, 206 days after implantation. The sutures are for the most part unabsorbed. They are surrounded by a layer of leucocytes and a thicker one of connective tissue. A precipitate of calcium salts (dark colored) may be seen on the periphery of the sutures in some places.

from Van Os and Michaël, the manufacturing process has been modified repeatedly. The conclusions mentioned in the present paper relate to a suture material which is not identical with that originally described by these authors, and for this reason some of my findings may differ from theirs.

The raw material for the new suture is tendon from slaughtered cattle, which can be obtained with less contamination than intestinal wall. The process itself destroys the few bacteria present, for the tendons are treated with acid, forming a viscous solution of pure collagen. This solution is spouted in ribbon form into an alkaline solution and the precipitated strands are dried and spun into threads. The breadth of the ribbons may be varied as desired from 2 to 25 mm. and the thickness

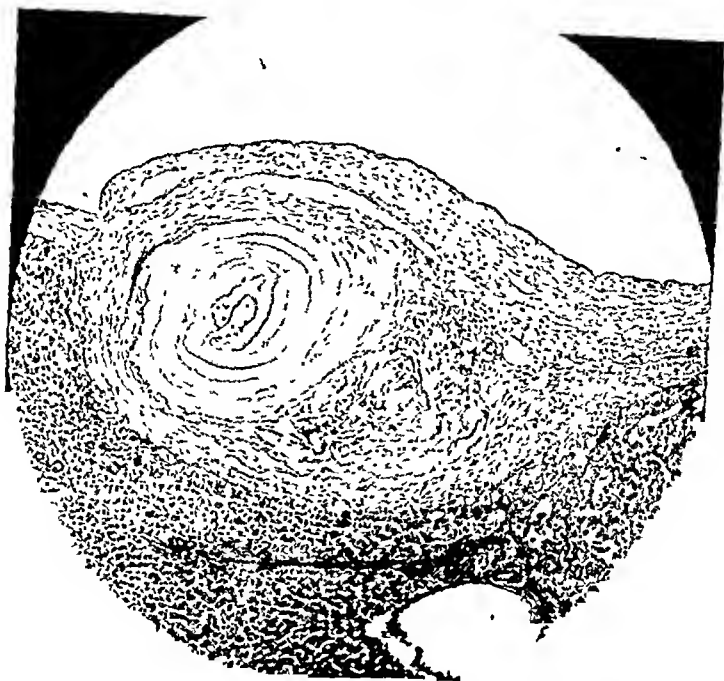


Fig. 4.—Collagen suture (No. 0 brocafil) on the surface of the liver, 107 days after implantation. There is a well-developed coat of connective tissue and the collagen is unabsorbed.

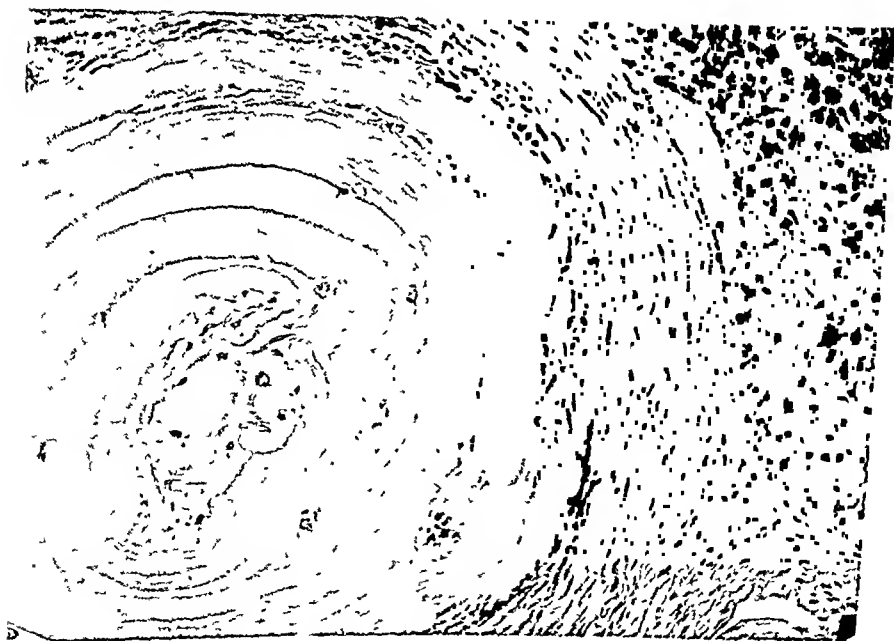


Fig. 5.—Same as Fig 4 with higher magnification. The connective tissue envelope is shown with peripheral connective tissuelike organization of the collagen substance. Fibroblasts have entered the strand through gaps in the collagen.



from 0.01 to 0.035 mm. Being satisfied with catgut at the time of the appearance of brocafil, at first I paid little attention to this new material, particularly since the first samples were brittle and difficult to handle, a fault which has now been corrected. However, I became interested in it for use as an absorbable tampon, an objective first suggested to me by the late Professor Lanz. In this connection a method was found to make a slightly denatured organic substance into tissues and membranes.<sup>4</sup> Later studies on collagen threads (brocafil) showed that the conclusions reached with tampons and membranes could not be applied unreservedly to sutures, as they possess somewhat different physical properties. In the past three years various collagen threads have been systematically studied.<sup>2</sup>

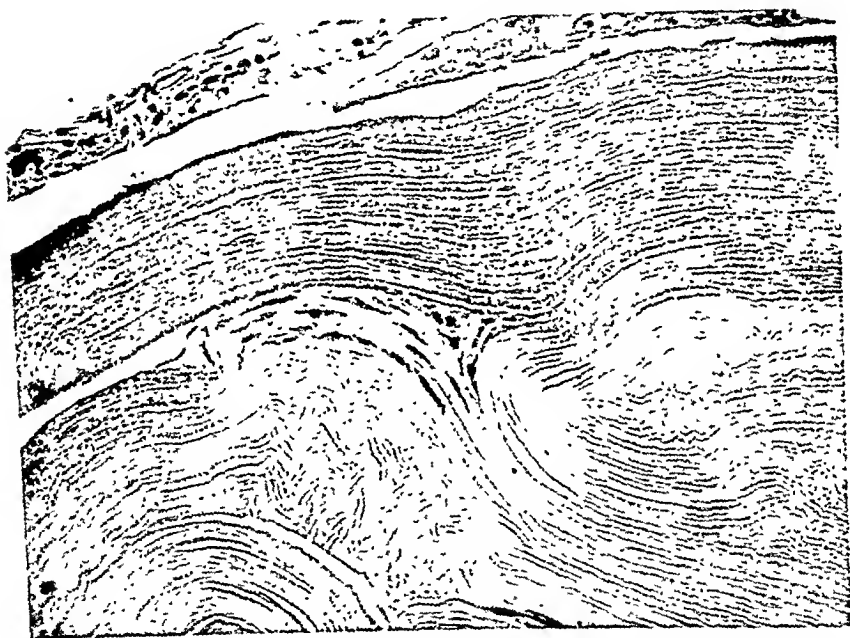


Fig. 6—Part of a No. 1 brocafil thread on the liver surface, 18 days after implantation. Beginning reoccupation of the collagen substance by connective tissue cells is shown. There is a slight digestion of the collagen on the surface and a giant cell may be seen.

The first collagen sutures proved brittle, breaking easily when knotted, and had an insufficient tensile strength, which diminished even more on contact with tissue fluids. These difficulties, however, were overcome by altering the process of manufacture.

The unexpected findings on microscopic examination of brocafil sutures previously placed in animal tissues were more disturbing. While

\*I wish to acknowledge the generous assistance given me by Professor Klarenbeek, of Utrecht, and Professor Heringa, of Amsterdam, while I was in their laboratories. Professor Heringa's advice, based on his considerable knowledge of collagens, was invaluable. The test material was provided by Messrs. N. V. Kon. Pharmaceutische Fabriek n. v. Brocades-Streeman & Pharmsaelt, Meppel, Holland. It was with their cooperation during these experiments that this investigation was successfully concluded.

it had been hoped that this would be an ideal absorbable suture material, it was found quite or nearly unchanged months after implantation, and at first even seemed to have a pronounced affinity for calcium salts. Modification of the preparation has failed to produce an absorbable suture.

Failure of absorption, although it has at first seemed a drawback, proved to be advantageous, for the collagen thread proved to be a material homogeneous with the tissues, which is accepted by the body almost without foreign body reaction. From the outset the extraordinary slightness of the reaction had been impressive and it became evident that this was the cause of failure of absorption of the sutures. As a

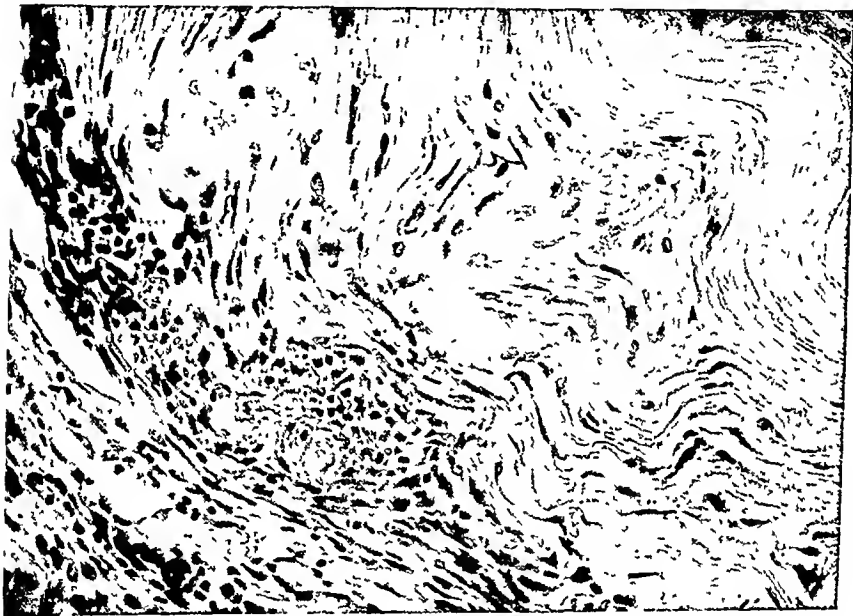


Fig. 7.—No. 0 brocafil in the liver, 107 days after implantation. Organization of the collagen material by young connective tissue is shown. Small foci of leucocytes on the periphery of the suture may be seen.

rule the tissues neither extrude nor destroy the collagen material, but rather an affinity between the collagen and the connective tissue cells of the neighborhood of the suture is manifest. Fibroblasts enter the clefts of the suture so that a condition develops which Nageotte calls "*la réhabilitation des greffes mortes*," the connective tissues inhabiting, as it were, the dead substance of the implant. The more numerous the clefts in the sutures, the more marked is this invasion of fibroblasts. The threads which have been tightly twisted to increase tensile strength offer little opportunity for penetration by connective tissue cells and remain more or less unchanged for a long time and can be differentiated from hyaline connective tissue bands only by their spiral and concentric structure. Thus, a kind of organization of the periphery gradually occurs.



Fig. 8—No. 000 brocafil suture in the abdominal wall, 42 days after implantation. There is rather marked reoccupation by connective tissue cells (*"réhabilitation"*). The suture is surrounded by a border of granulation tissue with some giant cells.

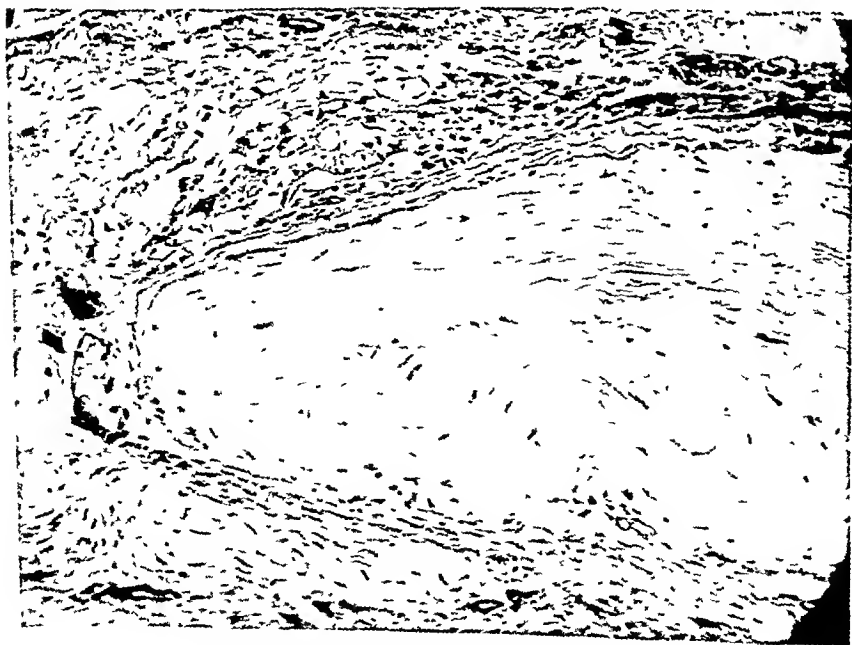


Fig. 9—Same as Fig. 8 with higher magnification.

At some points a very slight destruction of the collagen by mesenchymal giant cells and leucocytes may be observed and is immediately followed by the formation of young connective tissue. This organization with destruction of the implanted collagen is fundamentally different from the primary "*réhabitation*" of the implant by connective tissue cells, described above, for in the latter case the implant is accepted as part of the tissue. The presence of leucocytes about the collagen threads depends on secondary factors, such as wound infection, and use in the wound of iodine or other substances possessing an affinity for leucocytes. The greater the number of leucocytes, the greater will be the digestion and absorption of the implant.

The nature of the surface affects the fate of collagen implanted in the tissues. Thus, the smooth suture material, which offers little opportunity for invasion by tissue elements, resists destruction and organizing processes predominate. On the other hand, the rough collagen surface of tampons, for example, tends to imbibe serous fluid freely and be destroyed and absorbed. We, therefore, observe the remarkable fact that two implants consisting of the same material undergo entirely different fates, depending on their physical properties. The same is true of collagen membranes, for smooth parchmentlike membranes resist absorption and may be found almost unchanged after one and one-half years, when they resemble hyaline fascia, while the rough membranes, resembling tissue paper, are quickly invaded, partly destroyed, and partly organized.

Both kinds of collagen material are suitable for surgical use. Collagen suture, which is sufficiently developed for general use, cannot be likened to either silk or catgut but forms a new, third type of not entirely absorbable material which is nevertheless accepted by the tissues and converted to fibrous tissue strands. It may be used in hernioplasties, plastic procedures, and wherever permanence of the suture material is an advantage instead of a drawback.

In abdominal surgery collagen sutures are to be avoided, at least for the present, because here the strands, with their affinity for connective tissue cells, may give rise to neoplasms, an end result repeatedly observed in animals. Nevertheless, for muscle and fascial suture it possesses definite advantages over catgut, for catgut causes damage to these tissues and the growth of an abnormal scar tissue secondary to the serous and leucocytic infiltration it stimulates. Collagen sutures, on the other hand, are assimilated by the tissues and become a part of them by invasion by connective tissue cells, thus adding strength to the tissue. The introduction of collagen suture suggests the ideal of a selective specific ligature method. It would certainly be a definite improvement in surgical technique if for every tissue we could use the most nearly identical suture material: bowel wall substance (catgut) for bowel wall and connective tissue substance (brocafil) for connective

tissue. There is therefore every reason to accept the new collagen suture material along with catgut and silk.

To be sure, surgeons will have to become acquainted with this new material. In contrast to catgut it must be used dry, but, after some practice, it offers no more difficulties than other threads. It is adequate in tensile strength and security of knots, although the ends should be left as long as when catgut is used. In some respects suture technique will need to be adapted to the new suture material; where extra strength of the sutured tissue is required, as in hernioplasties, tendon repairs, and certain plastic procedures, collagen threads should not be used sparingly, but rather freely. Heretofore the rule has been to leave as little "alien" suture material in the tissues as possible, but now the coapted connective tissue will be best strengthened by a liberal use of collagen, tissue-forming threads. Catgut weakens connective tissue in the neighborhood of the suture, but collagen, applied so as to avoid tension necrosis, adds strength. These general rules may suffice, but the technique of collagen suture must be left to the surgeon in special cases.

#### SUMMARY

Little is known about the absorption of catgut. It has been shown to be very variable, in one instance being present 216 days after implantation in the liver of a rabbit. Catgut behaves as a foreign body in the tissues; although it is not extruded, it is either destroyed by a leucocytic reaction or encapsulated and impregnated with calcium salts. Catgut, therefore, does not "heal into" the tissues but is absorbed as a result of a local inflammatory reaction.

Brocafil, or collagen thread, on the other hand, is but slightly absorbed and primarily assimilated. This assimilation is:

1. Primarily an invasion of the suture by fibroblasts ("rehabilitation").

2. Secondly, a building of collagen connective tissue strands from the suture material.

Histologic studies indicate that the assimilation of brocafil, which occurs without inflammatory reaction, is preferable to absorption, which necessarily involves inflammation. Collagen suture is especially suitable for muscle and fascia apposition, hernioplasties, and plastic procedures. In the future more specific sutures will be possible, bowel wall substance (catgut) for bowel wall and connective tissue substance (brocafil) for connective tissue.

The author takes this opportunity to thank Dr. Clarence Dennis, of the Department of Surgery of the University of Minnesota, for reading the manuscript and improving upon the diction.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## A REVIEW OF THE PATHOGENESIS AND SURGICAL TREATMENT OF THYROID DISEASE

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WITHIN the past year the twenty thousandth thyroid operation was performed at the Lahey Clinic. It may be of interest in the light of this experience to review some of the more important clinical aspects of diseases of the thyroid gland as well as to present some of the recent developments relating to the pathogenesis of these conditions.

### PATHOGENESIS

The literature on the etiology and pathogenesis of thyroid disease is voluminous. An excellent review of the literature dealing with this phase of the subject was made in 1937 by Mahorner.<sup>1</sup> Since that time large numbers of articles have appeared dealing with the etiology of thyroid diseases, and these will be reviewed. Certain lines of investigation that were promising a few years ago have failed to live up to expectations; other work has been disproved by more recent investigators, and other so-called facts remain the center of considerable controversy.

The work of Marine,<sup>2</sup> Kimball,<sup>3</sup> and others, which indicates that endemic or simple goiter is a deficiency disease due to a lack of iodine in our food and drink, is supported by Eggenberger's<sup>4</sup> careful study of endemic goiter in the county of Vaud, Switzerland. He found that the goitrous counties north of Lake Geneva were not grouped geographically but according to the political boundaries of the county of Vaud. He found that from 1875 to 1891 the incidence of goiter was much less in the county of Vaud which used a salt containing iodine, than in the adjacent county of Fribourg which used an iodine-free salt. At the beginning of this century the former county which obtained its salt from its own salt mine in Bex began to refine its salt. As the salt began to contain less and less iodine, the incidence of goiter in Vaud increased. In 1924 iodine was added to the salt in the proportion of 5 mg. of sodium iodide to 1 kg. of cooking salt. At that time goiter was present in 77 per cent of the population, and in 1937, thirteen years later, this figure had dropped to 21 per cent. The greatest decrease was noticed in the nodular enlargements, not one of which was to be observed

in the school children in 1937. In Appenzell an iodized salt (10 mg. to 1,000 Gm. of cooking salt) was introduced in February, 1922. Here the best and most rapid results were noticed in the newborn. Owing to the use of iodized salt by the prospective mothers from the beginning of pregnancy (2,000 cases), no babies were born with goiter. Before this prophylactic measure was instituted, about 50 per cent of newborn babies in this district showed thyroid enlargement. Goiter during puberty did not appear in children who used iodized salt from the time of birth. The symptoms of cretinism also decreased in this same region. In army recruits the general growth was found to be much greater. The average height increased from 162 to 168 cm., and the chest expansion from 84 to 87 cm. between 1924 and 1938. According to Koller,<sup>5</sup> feeble mindedness and cretinism in children decreased from 1922 to 1937, as well as deafness and deaf mutism.

Eggenberger<sup>4</sup> also states that toxic adenoma was observed only in patients who did not use iodized salt regularly, and that the incidence of carcinoma of the thyroid gland seemed to increase at first, but after five years showed a remarkable decrease. That iodine deficiency may not be the only factor involved is indicated by the work of other observers. Lang<sup>6</sup> holds to the radioactivity theory and states that all other goiter theories lack consistency. He found that the disintegration of the uppermost strata of the soil produces radioactivity and that there is a definite parallelism between the intensity of emanation production and the incidence of endemic goiter and cretinism. Scott<sup>7</sup> feels that the element arsenic is probably a factor directly or indirectly concerned in the etiology of goiter, cretinism, and endemic deaf mutism. Wahlberg,<sup>8</sup> from a study of a map of goiter incidence in Finland drawn on the basis of medical examinations of conscripts, found that it coincided with a low iodine and high calcium content in the soil within the goiter area. He felt, however, that this did not prove a causal significance for either of these factors, but rather that the relatively rich occurrence of iodine outside this endemic area might have an inhibitory effect just as the rich deposits of calcium within it may have an aggravating influence on the disposition to goiter.

When we come to consider the etiology of hyperthyroidism, we find a picture that is even further from completion, in spite of the tremendous amount of work that has been done upon it. Out of this mass of evidence two facts seem fairly well established as being concerned in the production of hyperthyroidism. One factor, which Elmer<sup>9</sup> calls the external factor, is the hyperfunction of the anterior lobe of the pituitary gland. The other, or internal factor, is the insufficiency of the thyroid gland itself whereby it loses its ability to retain its elaborated hormone, thyroxine.

Collip<sup>10</sup> feels that the anterior pituitary has a twofold action on the thyroid, one which influences the secretion of the thyroid hormone and

the other which changes the morphology and size of the gland. Evidence has been introduced to show that these two normal influences can be separated from each other. It has long been known that the injection of anterior pituitary thyrotropic hormone in guinea pigs and dogs will temporarily raise the metabolic rate and give rise to the signs and symptoms of thyrotoxicosis. Thompson and his associates<sup>11</sup> found that patients with normal levels of metabolism could be made temporarily thyrotoxic and that in patients with toxic goiter the thyrotoxicosis could be made temporarily more severe. In six patients in whom this hormone was given for long periods, the basal metabolic rate, after an initial increase, dropped to a lower level than it had been initially, and was associated with a marked improvement in the patient. They feel, however, that at the present time the thyrotropic hormone does not have much value from the standpoint of routine therapy.

Elmer<sup>3</sup> succeeded in inducing experimentally a maintained hyperthyroidism in dogs and guinea pigs by injecting the thyrotropic hormone in increasingly larger doses. These dogs were characterized by a constantly elevated metabolism, a loss of weight despite an increased appetite, hyperiodinism, hypocholesterolemia, heart muscle damage, and histologically hyperfunctioning glands, seriously depleted of iodine. The anterior lobe of the pituitary in these dogs was almost completely deprived of acidophilic cells, which suggested to him that these cells were responsible for the production of thyrotropic hormone and that this appearance was due to the atrophy of disuse. He emphasized that the extensive liver damage constantly found in these experimental animals may prove to play a very important part in the pathogenesis of thyrotoxicosis. As he expressed it, the excessive production of the thyroid hormone by the thyroid gland and the slowing up of the destruction of the hormone by the liver result in an accumulation of the thyroid hormone in the body, with symptoms of thyrotoxicosis. He found no recent evidence to support the theory that hyperthyroidism is due to a disturbance in an equilibrium of thyroxine and antithyroid hormone, in which the thyroid hormone becomes predominant.

In this connection, Collip<sup>12</sup> states that it has been impossible up to the present time to produce inactivation, in human patients, of thyrotropic hormone, with any antihormone prepared so far. The antihormones that have been prepared which are able to neutralize human thyrotropic hormone are not suitable to give to human patients.

Elmer finds no recent evidence to support the theory of the secretion of an altered thyroid hormone as being responsible for thyrotoxicosis. He feels that the part played by the midbrain is limited, that the gonads, particularly the ovaries, exert their effect through the pituitary, and he rejects the hypothesis of a primary insufficiency of the adrenal cortex. Collip states that the functional and morphologic characteristics of the adrenal cortex are dependent upon the secretory action of the anterior



lobe of the pituitary. Bartels and co-workers,<sup>13</sup> from chloride depletion tests carried out on forty patients with hyperthyroidism, found nothing to support the theory that cortical hypofunction is a potent factor in causing hyperthyroidism.

Elmer also states that there is insufficient evidence for accepting the primary role of vitamin deficiency in this condition.

As for the role played by the sympathetics in the production of hyperthyroidism, Friedgood and Cannon<sup>14</sup> found that the cervical sympathetic trunks and the splanchnic innervation of the adrenals are not essential to the action of the anterior hypophyseal thyrotropic hormone. Brock and co-workers<sup>15</sup> found that bilateral cervical sympathectomy in rabbits caused a decrease in metabolic activity fairly uniformly, but stimulation of cervical sympathetic trunks did not cause an increase in the basal metabolic rate. The fact that the thyrotropic hormone acts directly on the thyroid without any intermediary has also been demonstrated by Eitel and his associates,<sup>16</sup> who found that an extract containing this factor when added to slices of dog thyroid increased the consumption of oxygen by the thyroid tissue and caused histologic changes similar to those usually seen *in vivo*.

#### BLOOD IODINE

A considerable amount of work has been done within the past few years upon blood iodine determinations in hyperthyroidism. This work has been found to have certain clinical applications. It is generally agreed that clinical hyperthyroidism is associated with the release of abnormal amounts of iodine from the thyroid, and many observers have drawn attention to the negative iodine balance which exists in this condition. In a clinical study of patients in 1936, Perkin, Lahey, and Cattell<sup>17</sup> found the iodine level of the blood elevated in 70 per cent of the cases of clinical hyperthyroidism and normal in the remaining 30 per cent. Perkin and Lahey<sup>18</sup> have since correlated the blood iodine level with the duration of symptoms in 305 cases of primary hyperthyroidism in which treatment had not been given. They found that the iodine level of the blood is elevated in the majority (86 per cent) of cases of hyperthyroidism in which the symptoms have been present for from one to nine months. The iodine level tended to fall within the normal range when the syndrome of clinical hyperthyroidism had been present for one year or longer. They point out that since in many cases the syndrome of clinical hyperthyroidism cannot be attributed solely to hypersecretion of iodine-containing products from the thyroid gland, other factors must be considered in the pathogenesis of the disease.

Perkin and Cattell<sup>19, 20</sup> carried this further in a study based on 256 cases of exophthalmic goiter and involving 833 blood iodine determinations. They divided their patients into three groups. In Group I they placed the 170 patients with an elevation of blood iodine before operation

the other which changes the morphology and size of the gland. Evidence has been introduced to show that these two normal influences can be separated from each other. It has long been known that the injection of anterior pituitary thyrotropic hormone in guinea pigs and dogs will temporarily raise the metabolic rate and give rise to the signs and symptoms of thyrotoxicosis. Thompson and his associates<sup>11</sup> found that patients with normal levels of metabolism could be made temporarily thyrotoxic and that in patients with toxic goiter the thyrotoxicosis could be made temporarily more severe. In six patients in whom this hormone was given for long periods, the basal metabolic rate, after an initial increase, dropped to a lower level than it had been initially, and was associated with a marked improvement in the patient. They feel, however, that at the present time the thyrotropic hormone does not have much value from the standpoint of routine therapy.

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lowing classification, based partly on structure and function and partly on clinical findings, has been found for many years to be very satisfactory to us in dealing with a considerable number of thyroid patients.

- I. Colloid goiter
- II. Adenomatous goiter
  - A. With secondary hyperthyroidism
- III. Primary hyperthyroidism
- IV. Adenoma
  - A. With secondary hyperthyroidism
- V. Carcinoma
- VI. Thyroiditis
  - A. Acute
    - 1. Suppurating abscess
  - B. Chronic
    - 1. Hashimoto type
    - 2. Riedel type
    - 3. Tuberculous
    - 4. Syphilitic
- VII. Myxedema
  - A. Spontaneous
  - B. Postoperative

I. *Colloid Goiter (Nontoxic, Diffuse, Physiologic, Adolescent).*—By this term we refer to a diffuse symmetrical enlargement without demonstrable clinical change in function. It is characterized by a simple hypertrophy of the gland with an increase in the size of the follicles and the amount of colloid storage. Hyperplasia is not marked and degenerative changes are absent. It is usually seen in girls from 9 to 18 years of age, although it is common in both sexes, and occurs at an earlier age where goiter is endemic. It may occur in adults at times of physiologic strain, such as during pregnancy, debilitating disease, or infection. The treatment is primarily medical and consists of improving the diet and hygiene of these patients by the administration of small amounts of iodine. Obviously, these patients should not be operated upon even when the goiter is associated with nervousness and emotional instability.

II. *Adenomatous Goiter (Diffuse, Nodular, Endemic, Colloid).*—This is a palpably nodular goiter, usually asymmetrical and often involving the entire gland. It probably starts as a colloid goiter in which localized areas of hypertrophy and hyperplasia have been followed by varying degrees of involution and degeneration. Thus it is characterized by fibrosis, cystic formation, cholesterol deposits, and even calcification. Histologically, it may show all the cellular changes that can occur in any type of goiter except the specific inflammations. It is an infrequent site of carcinoma, and in this connection it is important to distinguish it from the discrete or fetal adenoma. It is also important to remember that the two conditions may coexist. It is com-

and in whom the blood iodine fell to normal and remained normal after operation. The course of these patients was followed for one year; it was found that 90 per cent were completely cured, 15 patients or 8.8 per cent had transitory postoperative myxedema, and only 1 patient had recurrent hyperthyroidism. In Group II they placed the 61 patients with a normal preoperative blood iodine and a temporary postoperative increase in blood iodine. In this group 73.7 per cent were clinically cured, 3.3 per cent had transitory myxedema, and 19.7 per cent had persistence or recurrence of their hyperthyroidism. In Group III they placed the 25 patients who had a normal preoperative blood iodine value and no change in the iodine level following subtotal thyroidectomy. In this group, 96 per cent of the patients were clinically cured and 1 patient (4 per cent) had transitory postoperative myxedema. Since practically all the recurrent cases occurred in Group II and since there is a very low incidence of myxedema in both Groups II and III, they urged that a more radical thyroidectomy be done in these two groups; that is, in patients with a normal or low preoperative blood iodine level. They also point out that in long-standing cases the blood iodine level not only is normal but in most cases is uninfluenced by subtotal thyroidectomy, and they concluded that iodine metabolism as reflected by the blood iodine level is a secondary factor in these cases.

Hertz and associates,<sup>21</sup> in experiments with radioactive iodine, found evidence of a relatively high threshold for iodine uptake by the thyroid in hyperthyroidism. They felt that this might explain how a gland known to have a great affinity for iodine, as the thyroid does in this disease, still does not cure itself by taking up the small quantities of iodine normally found in the diet, but can be definitely benefited by the administration of a relatively large quantity of iodine.

It should be mentioned that several papers have appeared in the literature by McClendon<sup>22</sup> and others dealing with new and improved methods of blood iodine analysis. Many of them are excellent, but the apparatus still remains complicated and the technique involved. The work of Trevor<sup>23</sup> supports that of Perkin in showing that methods of alcohol precipitation do not recover thyroxine in the organic iodine fraction; whereas, methods of dialysis apparently do so.

#### CLASSIFICATION AND DIAGNOSIS

Before proceeding with a clinical discussion of thyroid disease, one must define the terms that will be used in order not to add to the confusion that already exists in the literature concerning the classification of thyroid disease. It is doubtful if any one classification of thyroid disease can be made that will be completely satisfactory to the surgeon, the internist, the pathologist, and the physiologist. At present, the fol-

It is obviously impossible to describe in detail the diagnosis and treatment of all these thyroid entities in the limited space available. The remainder of this paper will be limited to a discussion of those aspects of thyroid disease which are of particular interest to the surgeon.

#### ADENOMA AND ADENOMATOUS GOITER

It has been pointed out that the surgical problems associated with adenomatous goiter and the discrete adenoma resolve themselves into three main categories: first, the extrication of large adenomatous masses, frequently intrathoracic; second, the association of fetal adenoma and malignant degeneration; and third, the frequent association of secondary hyperthyroidism.

*I. Intrathoracic Goiter.*—Intrathoracic goiters are either outgrowths of adenomatous tissue from the lower poles of the thyroid gland or extrusions of true adenomas from the lower poles of the thyroid into the mediastinum. The attachment of the thyroid muscles to the sternum, and overlying the thyroid gland, serves to guide extruding adenomas into the superior mediastinum. These adenomatous masses, once lodged in the superior mediastinum, can increase in diameter only by descent, since the anteroposterior outline of the chest tapers inward from below upward. Over a period of years they may extend almost to the diaphragm. Before this occurs, however, they usually give rise to sufficient symptoms to force the patient to seek medical advice. The most important symptom is, of course, interference with breathing due to pressure on the trachea. Most intrathoracic goiters deviate the trachea laterally as the adenomatous mass tends to topple to one side or the other of the ridge-like trachea. On the other hand, adenomas arising particularly in the isthmus not infrequently descend behind the sternum so as to cause marked anteroposterior pressure on the trachea. For this reason all patients with an adenoma or adenomatous goiter, the lower border of which descends behind the sternum, should have lateral as well as anteroposterior roentgenograms of the trachea before operation. In many patients with intrathoracic goiters, the narrowing of the trachea with consequent increase in the interference with breathing can frequently be aggravated by flexion of the head, such as turning the head to the left when an intrathoracic mass on the left side has already stretched the trachea far to the right. In addition to tracheal pressure, the intrathoracic goiter will frequently produce a considerable amount of venous obstruction by pressure on the internal jugular veins. This may be manifested by the compensatory dilatation of the superficial thoracic veins, and occasionally when both internal jugular veins are compressed, by a "puttylike" edema of the face.

The dangers associated with the removal of intrathoracic goiters are associated with two fundamental problems: first, the maintenance of an

mon in regions where goiter is endemic. It is probably preventable by the administration of iodine, but after its development it is unaffected by medical treatment. The condition becomes surgical because of size, with pressure on the trachea and surrounding structures, because of its tendency to assume a substernal or intrathoracic position, because of the possibility of malignancy, and finally, because of superimposed hyperthyroidism. The last usually occurs some years after the development of adenomatous goiter. In this clinic the ratio of adenomatous goiter to adenomatous goiter with secondary hyperthyroidism is three to two. The actual difference is probably much greater since many individuals in the nontoxic group, being asymptomatic, do not seek medical advice.

III. *Primary Hyperthyroidism (Toxic Diffuse Goiter, Exophthalmic Goiter, Graves' Disease, Basedow's Disease).*—This type of thyroid disease, familiar to all, has made up approximately 50 per cent of the more than 20,000 thyroid operations performed in this clinic and forms the most important group, from a surgical standpoint, of all thyroid disease.

IV. *Adenoma (Discrete, Fetal).*—This is a discrete tumor separated from the rest of the gland by a definite fibrous capsule. It is probable that most of these tumors are of fetal origin, and the microscopic appearance may vary from the earliest fetal type of structure (cord and sheets of cells without follicle formation) to the most adult type of structure. Likewise, any degree of cellular change may be present, including hyperplasia, the various stages of degeneration, and malignancy. Because of the danger of malignant degeneration we feel very strongly that any adenoma, irrespective of size and irrespective of the age of the patient, should be removed.

V. *Carcinoma.*—These cases have been further subdivided for purposes of prognosis and treatment. Their management is a combined radiologic and surgical problem.

VI. *Thyroiditis.*—Acute thyroiditis is uncommon and is usually preceded by an upper respiratory infection. The gland is slightly enlarged, tender, firm, and may be associated with fever. It is usually accompanied by a sense of constriction in the neck, and pain on swallowing. Respiratory obstruction is uncommon. It usually subsides on conservative medical means, and only when abscess formation occurs is surgical treatment indicated.

Chronic thyroiditis is more common than and clinically must be differentiated from carcinoma. It may give rise to respiratory difficulty from tracheal constriction and it may be associated with hypothyroidism.

VII. *Spontaneous or idiopathic myxedema* is uncommon. Postoperative myxedema or hypothyroidism occurs in approximately 4 per cent of all patients submitted to subtotal thyroidectomy. The treatment of both is, of course, medical.

weeks or more, many of these patients will return with an accumulation of fluid in their mediastinal cavity.

It should be borne in mind that many of these intrathoracic goiters, with all their resulting problems, should never occur. If, as Lahey and others have repeatedly pointed out, every patient who has a goiter were examined once or twice a year, it could readily be determined whether an adenoma occupying the lower lobe of the thyroid was becoming intrathoracic, and its removal could be advised.

II. *Carcinoma of the Thyroid*.—As emphasized by Lahey, Hare, and Warren,<sup>25</sup> the logical approach toward decreasing the number of patients who lose their lives from malignancy arising in any given organ is, above any other consideration, concerned with the removal of pre-malignant lesions in that organ when such states are known to exist. The close association of adenomatous goiter and discrete adenoma with carcinoma of the thyroid is indicated in their study of 18,500 thyroid operations at the Lahey Clinic in which they found that 80 to 90 per cent of malignant tumors of the thyroid gland developed in pre-existing adenomas, usually in glands in which a single adenoma was present. In 10 per cent of all patients with a preoperative diagnosis of discrete adenomas and in 5 per cent of those with a preoperative diagnosis of adenomatous goiter, malignant degeneration was present at the time of operation. Brenizer and McKnight,<sup>26</sup> in a study of 84 cases of carcinoma of the thyroid, concluded that 80 per cent of all cases arise in pre-existing adenomas and that the incidence of cancer in true adenomas is about 8 per cent. Graham,<sup>27</sup> Crile,<sup>28</sup> and others feel that at least 80 per cent of all cancer of the thyroid arises in pre-existing adenomas. It has been repeatedly demonstrated that malignant degeneration may occur in an adenoma 1 cm. or less in diameter. Moreover, Pemberton,<sup>29</sup> Hare,<sup>30</sup> and others have called attention to the not infrequent occurrence of carcinoma of the thyroid in children and young adults. From all their observations one cannot emphasize too strongly that any adenoma or any mass that simulates an adenoma in the thyroid gland should promptly be removed. The all too common practice of advising these patients to watch their adenomas (or even to forget them), merely because the patient is less than 35 years of age or because the adenoma is small in size, should be vigorously condemned.

While the most satisfactory plan of surgery in the treatment of carcinoma of the thyroid lies in the removal of thyroid tumors before they become malignant, it should not be assumed that once suggestive evidence of malignant degeneration has occurred in an adenoma, the situation is hopeless. The stony hardness in one or both lobes of the gland is often due to thyroiditis rather than to malignancy, particularly if the symmetry and anatomical outline of the gland are preserved. The sudden enlargement and fixation of a previously freely movable adenoma

adequate airway while the intrathoracic mass is withdrawn from the chest; and second, the control of bleeding.

That dramatic moment when the surgeon, having mobilized the intrathoracic mass, was ready to deliver it through the narrow superior thoracic strait, knowing that for a few precious seconds the patient would be totally obstructed and knowing that wedging of the mass at this crucial period might spell disaster, has now largely been eliminated through the use of the semirigid intratracheal tube.

This is not to imply that the intratracheal tube has made anesthesia in these cases a simple matter. The introduction of the tube in a patient with a markedly deviated and narrowed trachea may tax the abilities of the best anesthetist. It is usually possible, however, with good exposure of the larynx by direct laryngoscopy and thorough cocaine-ization of the larynx and trachea, to insert the tube before starting the anesthetic, thus insuring an adequate airway from the very beginning, and avoiding the difficulty in getting these patients (with their narrow trachea) sufficiently anesthetized so that intubation can be done under anesthesia.

In spite of this help there are many intrathoracic goiters whose size makes it impossible to deliver them through the superior thoracic strait. Formerly this necessitated disarticulation of the clavicle and the removal of a portion of the manubrium. Lahey<sup>24</sup> has called attention to a valuable point in the handling of this type of case. He has pointed out that most of the intrathoracic goiters are soft and semicystic. Therefore, if the tumor is too large to be withdrawn easily through the superior thoracic strait, he incises the capsule, thrusts a finger into the center of the tumor, breaks up the center, and aspirates the contents with the suction tube. The shell of the adenoma is then withdrawn without difficulty. In an experience with over 300 completely intrathoracic goiters he has rarely found it necessary to remove the manubrium except when the mass is carcinomatous and the center may be solid.

The control of bleeding is not difficult when it is realized that every intrathoracic goiter gets its blood supply from above; that is, from the superior and inferior thyroid arteries which it carries with it as it descends into the thorax. If these are ligated, together with the superior, middle, and inferior thyroid veins, before manipulation of the tumor is attempted, the danger of uncontrollable bleeding is slight. All this presupposes adequate exposure of the field of operation, and there can surely be no argument regarding the advisability of the bilateral division of the prethyroid muscles in these cases.

One other point to which attention has been called in the last few years is the length of time of postoperative drainage indicated following the removal of an intrathoracic goiter. The cavity which remains cannot be obliterated except by the gradual expansion of the lung and pleura. If the postoperative drainage is not prolonged, that is, three



in these tumors of lateral aberrant thyroid origin which recur locally so frequently and metastasize so infrequently. It is generally agreed today that the treatment should consist of radical dissection of the neck plus the removal of any similar tumors in the thyroid gland. If malignant degeneration has occurred in any of these tumors, the operative procedure should be followed by x-ray therapy.

One cannot leave the subject of thyroid carcinoma without emphasizing one important technical point which has been appreciated within the past few years. Graham<sup>27</sup> has pointed out the tendency for recurrent thyroid malignancy to extend within the thyroid veins, thus indicating the necessity of a wide and radical removal of the adjacent veins along with the tumor itself. By ligating and dividing the internal jugular vein high and low in the neck, the entire vein along with its tributaries (the superior, middle and inferior thyroid veins), the accompanying lymph nodes, and the tumor can all be removed in one piece.

III. *Secondary Hyperthyroidism*.—There is an almost universal tendency today to regard all cases of hyperthyroidism, both primary and secondary, as representing a single disease. Therefore, the association of adenoma and adenomatous goiter with secondary hyperthyroidism will not be discussed apart from hyperthyroidism in general except to call attention to two outstanding clinical differences. The patients with secondary hyperthyroidism may respond less well to iodine medication and to preliminary pole ligation than do patients with exophthalmic goiter. Moreover, possibly due to their more advanced age with resultant damage to vital organs, they present a definitely greater operative risk.

The operative mortality at the Clinic in exophthalmic goiter is 0.66 per cent. The case mortality is 0.91 per cent (the two figures are of course due to the fact that many patients had more than one operation; this also includes recurrent hyperthyroidism). In adenomatous goiter with secondary hyperthyroidism, however, the operative mortality rises to 2.30 per cent and the case mortality to 2.73 per cent.

#### HYPERTHYROIDISM

Of the 20,000 thyroid operations that have been performed at the Clinic, approximately 76 per cent were on patients suffering from hyperthyroidism. The great majority of goiter patients in our section of the country, at least, fall into the primary hyperthyroidism or exophthalmic goiter group. We are quite convinced, however, that the type and severity of hyperthyroidism vary markedly in different parts of the country, a fact which must be kept in mind in the evaluation of thyroid statistics.

*Diagnosis*.—The classical description of hyperthyroidism is so well known that it needs no repetition. I will merely mention certain points

may be due to hemorrhage into the adenoma rather than malignant degeneration, particularly if there is localized pain and tenderness associated with it. Even when malignant degeneration has occurred it may not have penetrated the capsule of the adenoma or it may have eroded the capsule and invaded the gland at only one point. Radical operation combined with radiation, which is generally recognized today as the most satisfactory form of treatment for thyroid malignancy, will save the majority of these patients. Lahey, Hare, and Warren,<sup>25</sup> in a study of 231 cases of cancer of the thyroid gland, found a five-year survival rate of 71 per cent in cases of malignant adenoma with blood vessel invasion. The rate was even higher in papillary adenocarcinoma (80 per cent) and was least favorable in diffuse alveolar, small round-cell and giant-cell carcinoma. Pemberton,<sup>29</sup> in a study of 774 cases of malignant lesions of the thyroid gland, found the same variation as regards the type of malignancy, with a five-year survival rate of 70 per cent and a ten-year survival rate of 58 per cent for all cases.

Even when dealing with extensive and apparently hopeless malignant disease, it is wise to obtain a biopsy specimen for pathologic examination, since the degree of radiosensitivity is known to vary markedly with the different types of thyroid carcinoma. If the tumor is radiosensitive, much can be done for these patients in the way of relief of symptoms and prolongation of life. Nor is a poor prognosis to be given in a case in which there is a nodule in one lobe of the thyroid plus several (questionable metastatic) palpable nodules along the great vessels of the same side. As a matter of fact, such a case will probably fall in the group of patients with the most favorable prognosis of all thyroid malignancies; that is, the papilliferous tumors of the thyroid, including those of aberrant thyroid origin. These usually occur in patients under 40 years of age and are five times more frequent in women than in men. They must be differentiated from tuberculous adenitis, lymphosarcoma, and other tumors by biopsy and microscopic examination. Cattell<sup>31</sup> reported 30 cases with lateral aberrant thyroid tissue in which one-third showed a similar but quite separate involvement of the thyroid lobe on the same side. In all, the aberrant thyroid tissue was removed surgically and post-operative radiation therapy was given to all who showed malignant change. A follow-up examination of these patients revealed that 20 had no recurrence; 4 had recurrence but have remained well after a second operation. Four patients have died of proved cancer. One patient died of recurrent malignant disease of lateral aberrant thyroid origin. One patient had had repeated pathologic fracture of the right humerus, and another, metastasis to both lung fields. Ward<sup>32</sup> also found 2 deaths from papillary tumor in aberrant thyroid tissue, 1 from local recurrence and 1 from pulmonary metastasis. This would seem to indicate a somewhat more guarded prognosis than was at first thought indicated

will simulate those of hyperthyroidism even more closely. These patients have a feeling of warmth, perspire readily, often have a rapid pulse and are emotionally unstable. The hypertension alone will frequently give patients a warm moist skin and a sensation of warmth. They have an active heart with forceful sounds and may even have a suggestion of exophthalmos. The menopausal patient will usually show no weight loss unless the appetite is very poor, and any tremor present is apt to be gross and inconstant. In the hypertensive patient the diastolic pressure is usually elevated; whereas, a diastolic pressure over 100 is unusual in pure hyperthyroidism. These patients will frequently show a false elevation of the basal metabolic rate at the first test, especially if the test is done when they are outpatients. Even when the patient is at bed rest in the hospital it may require two more readings to get the true basal metabolic rate. Any patient who has auricular fibrillation, whether temporary or permanent, in a heart without valvular lesion or other definite damage, should be considered as a patient with hyperthyroidism until this is ruled out. Even when organic heart disease is present, superimposed hyperthyroidism may be the factor which initiates the fibrillation. The tremendous improvement that subtotal thyroidectomy will produce even in this last group of patients makes it very important that this factor not be overlooked. When the auricular fibrillation is associated with cardiac failure, the gradual collection of edema may mask a marked loss in weight due to the hyperthyroidism. Leucemia, diabetes, tuberculosis, and rheumatic infection may at times simulate hyperthyroidism but the other factors involved will usually reveal the diagnosis. It is also to be remembered that when diabetes or tuberculosis coexists with hyperthyroidism, correction of the hyperthyroidism greatly improves the associated condition.

*Pathologic Physiology.*—The pathologic physiology, in so far as we understand it today, has already been discussed under the pathogenesis of the disease. Mention will be made here of other interesting observations along this line which have been made in the past few years. We know that there is a reduction in plasma cholesterol in the majority of cases of clinical hyperthyroidism and that this returns to normal following the relief of the hyperthyroidism. We also know that there is an abnormal elevation in plasma cholesterol in cases of clinical myxedema and that this furnishes us with one of our best diagnostic tests for this condition. This also falls to normal following the feeding of desiccated thyroid. Hurxthal and Perkin,<sup>33</sup> by feeding thyroid extract to mice, found that the decrease in the body content of cholesterol was not due to an increase in excretion of the cholesterol but to an actual destruction of the total body cholesterol. They also found that there appeared to be a specific optimal dose of desiccated thyroid effecting optimal destruction of cholesterol.

which we feel have been helpful in the recognition of the less obvious cases and in the differentiation of conditions which may closely simulate hyperthyroidism.

While loss of weight is one of the most common symptoms of hyperthyroidism, when it has been accompanied by a poor appetite from the beginning it is usually not due to hyperthyroidism. Exophthalmos, another outstanding symptom of hyperthyroidism, while present in only 50 per cent of the cases, is still many times more frequent in this condition than in any other disease. When it is present, even if unilateral, hyperthyroidism must be ruled out.

Certain symptoms are important because of their absence. A fine tremor and a palpable heart thrust may occur in purely nervous individuals as well as in patients with hyperthyroidism, but their absence is indicative of little thyroid overactivity. Patients suffering from "neurasthenia" or neurocirculatory asthenia usually feel ill; whereas, the average patient with hyperthyroidism feels fine, particularly when resting. The hands and feet of the neurasthenic are usually cold and moist, in contrast to the warm, moist hands and feet of the hyperthyroid patient. Although warm moist skin, sensitivity to heat, and other signs of increased circulation are characteristic of thyrotoxicosis, it must be remembered that the elderly patient who does not have the capacity to react vigorously to hyperthyroidism may not exhibit these signs and symptoms. These patients often present a picture aptly described as apathetic hyperthyroidism. In these patients, who may show little else except an increased pulse rate and an unexplained loss of weight, the diagnosis may easily be overlooked. Frequently, when the diagnosis is made, the seriousness of the condition is not appreciated, and an unexpected fatality is the result of a subtotal thyroidectomy.

The blood pressure in hyperthyroidism is usually moderately elevated, but the loud and snapping sounds heard in the stethoscope as the mercury in the sphygmomanometer approaches the level of the diastolic pressure are even more characteristic and important. Except for hyperthyroidism it is only present in aortic regurgitation and marked arteriosclerosis. Congestive heart failure may occur in this condition if auricular fibrillation or organic heart disease is present, but congestive failure with normal rhythm and no demonstrable cardiovascular disease is very rare in hyperthyroidism. Enlargement of the thyroid gland or goiter is usually present but is not necessarily visible, and may only be detected by careful palpation. A change in consistency even when the size appears normal will usually be detected on careful palpation. The hyperplastic gland is firmer than normal, and after the administration of iodine the firmness may approach hardness. While the group of patients designated as having neurocirculatory asthenia form the largest group in which hyperthyroidism must be ruled out, the symptoms of hypertension, especially when associated with menopausal symptoms,

cites particularly the type of case in which, on the initial dose of iodine, the basal metabolic rate has dropped to a substandard level. We believe that in this type of case one would have to be very certain that the patient had hyperthyroidism in the first place, and second, that the apparent cure was maintained over a period of years.

A review of the recent literature would indicate that roentgen therapy as a method of treating hyperthyroidism is being used less and less frequently. Certainly it is true that those surgeons and physicians most familiar with this disease have never felt that the results of roentgen therapy would compare with the results obtained from radical operation. Even in the poor-risk, severely toxic patient, Pemberton<sup>41</sup> believes that a preliminary pole ligation or lobectomy is preferable to x-ray treatment. The majority opinion certainly supports this view. Means feels that x-rays should be used routinely for recurrent hyperthyroidism. We believe that this method of treatment may be justifiable if the thyroid remnants are small. It should also be pointed out that anyone familiar with thyroid surgery has frequently been surprised at the rather large size of the remnants as disclosed at operation in cases in which little could be palpated preoperatively.

*Treatment.*—There has been no radical change in the preoperative preparation of hyperthyroid patients within the past few years beyond perhaps the administration of additional amounts of protein and vitamin B. Our main reliance is still on iodine, and most authorities agree that its maximal effect is obtained in eight to fourteen days. While bed rest is the other mainstay in the preoperative period, allowing the patients to move about a little during the last few days before operation is probably better, from a circulatory standpoint, than is complete bed rest.

The question of anesthesia in these patients is still a matter of opinion. Many surgeons still prefer local anesthesia, feeling that it is the safest of all anesthetics. This point could only be proved by comparing mortality figures of a large series of comparable cases in which operation was performed under local anesthesia and under other methods of anesthesia. We feel that this point has not been proved, and that patients with hyperthyroidism are not as well able to withstand the emotional ordeal of a major surgical procedure awake and conscious as any other type of patient. We doubt if there is any combination of narcotics and other drugs which can be used in safe doses and yet insure that the patient will not remain awake and keenly conscious of what is going on. Ether is associated with a prolonged induction period and frequently followed by vomiting, a very undesirable complication in the immediate postoperative period of these patients. Nitrous oxide we feel must be used with too little oxygen (usually 10 per cent) for use in patients in whom oxygen demands are two to three times that of the average patient. Avertin, which is frequently used with nitrous oxide,

More evidence of the important role played by the liver in this condition was found by Bartels<sup>34</sup> in his studies on the serum protein in hyperthyroidism. He had previously noted that the degree of disturbance of liver function, as determined by the hippuric acid test, is in direct relation to the severity of the hyperthyroidism as determined by the basal metabolic rate, and the clinical opinions as to the necessity for a one- or two-stage operation. He found that there was a rough correlation between the level of the total serum protein and the excretion of hippuric acid used as a test of hepatic function. In 73 per cent of the cases in which the value for the total serum protein was below 6 Gm., a two-stage operation was required, and in all cases in which the serum albumin content was 3 Gm. or less two-stage operations were required. Bartlett<sup>35</sup> has pointed out that blood amylase, another indication of liver function, is decreased as thyroid activity increases. Crile, Jr.,<sup>36</sup> found that liver function tests indicated that liver function was most impaired in elderly patients with hyperthyroidism, and believes that liver failure is the most common cause of delirium and confusion following operation on these patients.

Shaffer,<sup>37</sup> in a study of the liver from 24 fatal cases of toxic thyroid disease, found a loss of liver weight, fatty infiltration, cirrhosis, and lymphocytic infiltration in the periportal region often associated with patchy fibrosis. He found these lesions much greater in frequency and severity than in a carefully studied group of 100 control cases.

Means<sup>38</sup> feels that there is good reason to suspect that most patients with hyperthyroidism suffer from a relative shortage of vitamin B. Drill and Hays<sup>39</sup> found an increased requirement for vitamin B in experimental animals with hyperthyroidism and suggested that a subnormal amount of vitamin B in the diet may be at least partially responsible for abnormal liver function in this disease. These studies would indicate that a high protein diet with supplementary vitamin B, in addition to large amounts of carbohydrate and iodine, might well be used in the preoperative preparation of patients with hyperthyroidism.

Little need be said regarding the great value of iodine in the preoperative preparation of these patients, for it has long proved its worth. Cutting and Kuzell,<sup>40</sup> in experimental hyperthyroidism produced by the injection of thyrotropic hormone in guinea pigs, found that only sodium iodide would limit consistently the increased metabolic rate. Sulfanilamide and phenobarbital reduced the degree of hyperthyroidism by a general depressant action only, and testosterone and calcium gluconate did not affect it at all. Most authorities condemn the long-continued use of iodine without operation in hyperthyroidism. The beneficial effect is eventually lost in the vast majority of patients and then a preoperative improvement can no longer be obtained by the use of iodine. This is the so-called iodine-fast patient. Means, however, feels that a few selected cases of hyperthyroidism may be treated by iodine alone. He

An apparently uneventful course should not tempt the operator into doing a complete operation on a patient in whom the age, toxicity, and preoperative course would seem to make hemithyroidectomy advisable. The converse of this, of course, is not true. Occasionally a patient in whom a subtotal thyroidectomy had seemed indicated, by an increased consumption of oxygen, a widening pulse pressure, and rising pulse rate, will warn the alert operator to be content with hemithyroidectomy.

The necessity of adequate exposure has been repeatedly emphasized in the last few years. With adequate exposure by means of a high elevation of the flap, division of the prethyroid muscle, and the complete lateral dissection of the gland, uncontrollable hemorrhage should never occur and parathyroid tetany and recurrent laryngeal nerve injury should be reduced to a minimum. The prophylaxis of these two complications is far more satisfactory than their treatment, and the prophylaxis is based largely on adequate experience and a dry operative field.

*Postoperative Complications.*—The most important complication which is likely to occur in the first twenty-four hours following operation is respiratory obstruction. When the obstruction is due to a profuse hemorrhage from the superior or inferior thyroid arteries, the clinical picture is dramatic and calls for immediate treatment. The incision must be opened on the spot without regard for asepsis, the prethyroid muscles separated, the clot quickly evacuated, and a gauze pack inserted until the patient can be brought to the operating room and the bleeding vessel ligated. Prompt action of this sort has saved more than one life in the past.

Much more frequent is the partial obstruction due to laryngeal edema or paralysis of the vocal cords. Because the cyanosis and other signs of respiratory obstruction are much less marked, they are frequently overlooked. Yet the end results of this type of obstruction may be just as serious as when due to profuse hemorrhage. Nurse, intern, and surgeon must be on the alert for mild degrees of cyanosis and early signs of obstruction. If these signs are present, the patient must be watched very closely and if they show any tendency to persist or increase or if there is any question of the patient's receiving an adequate supply of oxygen, tracheotomy should be promptly performed. Delay in these patients is serious. Pemberton has said, when in doubt, do a tracheotomy at once. Lahey has pointed out that patients with a slight cyanosis as a result of tracheal obstruction, who are permitted to go through the night suboxygenated and then have a tracheotomy performed the following morning, frequently continue to sink into unconsciousness and die.

The next important complication which may occur in the postoperative period is the development of thyroid crisis. Here again, as in other complications of thyroid surgery, prophylaxis is much more satisfactory than treatment. The careful preparation of these patients, and particularly the accurate estimation as to the amount of surgery each

in addition to being a respiratory depressant, has, in the experience of Cole and Brunner,<sup>42</sup> occasionally aggravated the toxicity in severely toxic patients. The first answer to this increased demand for oxygen in the anesthetic mixture came with the introduction of ethylene in 1924. With this gas, a higher concentration of oxygen could be used (15 to 20 per cent) and it has been a very satisfactory form of anesthesia in thyroid surgery. Cole and Brunner<sup>42</sup> feel that it is the anesthesia of choice. With the introduction of cyclopropane in 1937 it became possible to administer 50 to 85 per cent oxygen in the anesthetic mixture, and for many years we have felt that it is the best single anesthetic for use in hyperthyroidism. There is a tendency, however, to cardiac irregularities, especially in patients with coexisting heart damage with the use of cyclopropane in higher concentrations and this has led to the latest development in general anesthesia for toxic patients. Smaller concentrations of cyclopropane are used and the anesthetic mixture is frequently diluted with moderate amounts of ethylene, and even small amounts of ether whenever there is any tendency to cardiac irregularity or in patients with known cardiac damage. Cyclopropane-oxygen is an explosive mixture (although no more so than nitrous oxide-oxygen, ether or ethylene-oxygen mixture) and a considerable amount of work has been done in the last few years upon eliminating this hazard. Woodbridge, Horton, and Connell<sup>43</sup> have discussed the prevention of static spark and have described an intercompler now installed on all our anesthetic machines which may prove to be the answer to the anesthetic explosive hazard.

For many years we have been convinced that there are patients with thyrotoxicosis who, no matter how carefully prepared, will not stand subtotal thyroidectomy, but who will stand hemithyroidectomy. We are also convinced that a few patients will survive hemithyroidectomy only if first submitted to preliminary pole ligation. Continued experience has given us no reason to change these convictions despite frequent statements of a contrary nature which appear from time to time in the literature. Approximately 20 per cent of our toxic patients are operated upon in two or more stages. Marshall<sup>44</sup> found that a drop in the metabolic rate, a drop in pulse, and a gain in weight occurred in 85 per cent of patients following a first-stage hemithyroidectomy, and in 66 per cent following preliminary pole ligation. The elderly patient, those in whom the disease has been present for over a year, the severely toxic, the patient who has lost 50 pounds or more in weight, the patient with toxic symptoms of the gastrointestinal tract, the patient who fails to gain weight in the hospital—all carry an increased operative risk. If such a patient fails to survive a subtotal thyroidectomy, the surgeon must in all fairness assume that this patient might have survived a less extensive procedure. The patient's course on the operating table is only one of the factors in evaluating the risk of a subtotal procedure in any given case.



dyspnea of these patients but leaves them with a limited voice. Another more recent operation has been devised by King,<sup>47</sup> by means of which the arytenoid cartilage is loosened and then fixed in a lateral position by attachment to the thyroid cartilage. This also has restored an adequate airway to these patients, and may prove to leave them with a better voice than does the submucous resection of the cords.

Persistent hyperthyroidism must, in most cases, be considered as due to a failure to remove sufficient thyroid gland at the original operation. The cause of recurrent hyperthyroidism is unknown; it is most likely due to the same factors which produced the original disease. Cattell and Morgan,<sup>48</sup> in a study of 4,456 cases of exophthalmic goiter, found the incidence of persistent hyperthyroidism to be 2.4 per cent and recurrent hyperthyroidism to be 3.7 per cent (306 cases in all). These cases were followed for a period of from two to twelve years. Collier and Potter<sup>49</sup> reported 267 cases of exophthalmic goiter with a recurrence rate of 4.8 per cent. Joyce<sup>50</sup> found a recurrence rate of 5.7 per cent in toxic goiter, and Berlin and Gargill<sup>51</sup> found an incidence for persistent and recurrent hyperthyroidism of 5.2 per cent. There seems to be a general agreement that certain cases, especially mild cases, can be controlled on iodine therapy alone or in conjunction with radiation. There is also, however, a general agreement that the treatment of choice for the more severe case, especially when the remnants are enlarged, is subtotal excision of the thyroid remnants. This agreement exists in spite of the fact that all of the complications found after primary operation for hyperthyroidism occur in a considerably higher percentage after secondary operations.

#### SUMMARY

A review of recent developments relating to the pathogenesis of diseases of the thyroid gland has been presented. In addition, certain factors in the diagnosis and treatment of these conditions have been discussed, which, in the light of our experience at the Clinic, seem particularly significant from the point of view of the surgeon.

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individual patient will tolerate are our best protections against thyroid crisis. Careful sedation, oxygen, Lagol's solution and ample amounts of intravenous fluids and glucose in the first forty-eight hours following operation will control most of the postoperative reactions which occur in these toxic patients.

Postoperative tetany is a distressing complication which, thanks to adequate exposure and careful preservation of the parathyroid glands, is becoming less and less common. Out of 20,000 thyroid operations at the Clinic there have been but ten cases of established tetany. Calcium gluconate by vein and calcium lactate and dihydrotachysterol (A.T.10) by mouth will control most of the transient cases very satisfactorily.\*

A similar situation exists in regard to paralysis of the recurrent laryngeal nerves. In 1926, at Dr. Lahey's<sup>47</sup> suggestion, the routine exposure of the recurrent laryngeal nerve in all thyroid operations was started at the Clinic. With adequate exposure, its visualization and the accurate determination of its position add but a few minutes to the operative procedure. With the nerve under direct vision, the radical resection of thyroid tissue, whether malignant or benign, may be carried out with far greater ease of mind than when one is merely hoping that the nerve will not be caught in the dissection or involved in the resulting scar. Certainly, the routine exposure of the recurrent laryngeal nerve has definitely decreased the percentage of nerve injury in our hands. Even those who feel that it is not necessary to visualize it in all cases must agree with Cutler that any surgeon doing thyroid surgery must visualize it in a sufficient number of cases to be perfectly familiar with its usual position. Moreover, in cases in which it is apt to be out of its usual position, as in adenomatous goiter, it would seem advisable to expose the nerve and to know where it is rather than to assume it is in its normal position. It is generally agreed today that the nerve can be exposed completely in its cervical course without harm to the nerve or patient.

While an injury to one nerve is unfortunate, the injury of both recurrent laryngeal nerves is a serious surgical calamity. There is at first loss of voice, still with normal ability to breathe, but within a few months, although the voice returns, there is increasing difficulty in breathing, because of the constant narrowing of the glottic space from fibrosis of the cords and fixation of the arytenoid cartilages. This narrowing may become so marked that the necessity for a tracheotomy becomes urgent. Two operations have been devised which offer adequate relief to these unfortunate individuals. That of Hoover,<sup>48</sup> now well tested over a five-year period, consists in the submucous excision of one cord by a laryngofissure, thus leaving an adequate airway through a space lined with mucosa. This relieves completely the incapacitating

\*We have recently obtained equally satisfactory results with vitamin D<sub>2</sub> used in place of A.T.10, along with calcium lactate, in the treatment of chronic tetany.

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reversed by the addition of an excess of nicotinamide, the active compounds apparently competing with nicotinamide for the enzyme or enzymes. Sulfanilamide, on the other hand, does not possess this specific activity, but causes only a small inhibition unrelated to the nicotinamide stimulation. These workers, therefore, postulate that sulfapyridine may owe its therapeutic activity to two different groups, namely, the sulfanilamide group which causes the nonspecific inhibition obtained with sulfanilamide, and the pyridine group which specifically inhibits the activity of the enzymes associated with nicotinamide and related compounds, and they suggest that this twofold activity of sulfapyridine may account for the greater efficiency of this compound over sulfanilamide in the treatment of a number of diseases. Sulfathiazole acts in a manner similar to that of sulfapyridine.

Elizabeth M. Cranston, of the University of Minnesota, compared the pressor effects and toxicity of ephedrine and racephedrine (the racemic mixture of d and l ephedrine). The LD 50 for intravenous injection in normal rabbits was 60 to 70 mg/kg for ephedrine and 90 mg/kg for racephedrine. In barbitalized rabbits, ephedrine intravenously produced a greater rise in blood pressure than racephedrine in equal doses, but the toxicity was the same for both drugs, early toxic symptoms appearing with 20 mg/kg, and 60 mg/kg killing four out of five animals. T. J. Becker, M. R. Warren, D. G. Marsh, and R. S. Shelton, of the Research Laboratories of the Wm. S. Merrell Co., reported a study of a new ephedrine compound, nethamine hydrochloride (levo-N ethyl ephedrine hydrochloride). The MLD following intravenous administration to rabbits was 50 mg/kg, or approximately the same as that of l ephedrine. Prolonged daily administration in doses of 25 mg/kg intravenously or 50 mg/kg orally produced no apparent pathologic changes. Very little central stimulation results from administration of the drug to rats. The pressor effect of this compound is about one tenth the pressor action of similar amounts of l ephedrine. In perfusion experiments l-N ethyl ephedrine and l ephedrine were found to relax normal bronchioles to approximately the same degree. Strips of isolated rabbit small intestine were usually relaxed by l-N ethyl ephedrine, but at times a stimulation was produced. Preliminary experiments on the stomach *in situ* indicate that the substance produces a definite inhibition of gastric peristalsis.

The importance of the autonomic nervous system in the action of morphine was again stressed in a number of papers. C. I. Wright, of the National Institute of Health, reported on the inactivation of choline esterase by morphine and some of its derivatives. Increasing concentrations of morphine, dihydrid and dihydrodesoxymorphine D produced increasing inactivation of the choline esterase of dog serum and rabbit brain. The inactivation produced by dihydrodesoxymorphine D was much greater than that produced by either morphine or dihydrid, being 69, 45 and 44 per cent respectively for a drug concentration of 0.33 mg/cc. D. H. Slaughter, C. R. Treadwell, and J. W. Gales, from Baylor University, reported on some relationships between morphine and the cholinergic drug prostigmine methyl sulfate. They found that the administration of 0.1 mg/kg of prostigmine methyl sulfate to morphine addicted dogs during the withdrawal period following prolonged administration of three daily subcutaneous doses of 20 mg/kg of morphine sulfate resulted in a more rapid disappearance of the morphine from the blood stream, a 19 per cent decrease in the excretion of morphine, and a decrease in the severity of the withdrawal symptoms. These workers have also found that the analgesic action of morphine is enhanced by the simultaneous administration of certain cholinergic drugs. The administration of prostigmine simultaneously with a half dose of morphine produced an analgesic effect equal to that of a full

# Review of Recent Meetings

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## REPORT ON THE MEETINGS OF THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC., CHICAGO, ILL., APRIL 15-19, 1941

HAROLD N. WRIGHT, PH.D., MINNEAPOLIS, MINN.

*(From the Department of Pharmacology, the University of Minnesota  
Medical School)*

AT THE thirty-second annual meeting of the American Society for Pharmacology and Therapeutics in Chicago, April 15 to 19, 1941, some 108 papers were presented. Among the more important papers of interest to the surgeon were the following:

At the joint session of the Federation of American Societies for Experimental Biology, E. K. Marshall, Jr., from Johns Hopkins University, discussed the work which he and his collaborators have done with sulfanilylguanidine, a chemotherapeutic agent of the sulfonamide series recently introduced for the treatment of intestinal infections. Sulfanilylguanidine is water soluble to a considerable degree, yet poorly absorbed from the intestine. The use of intestinal antiseptics heretofore has depended upon low water solubility to avoid absorption. The idea of a drug which is fairly water soluble and therapeutically active but not absorbed from the intestine presents a new principle in the use of the new bacterial chemotherapeutic agents; the fundamental principle involved is the achievement of a high concentration of the drug in the intestine and a low concentration in the blood and tissues. The acute toxicity of sulfanilylguanidine by mouth is very low, probably due to poor absorption. Continuous administration in mice and rabbits indicates that it is probably less toxic than sulfapyridine and sulfathiazole. Favorable results were reported of the clinical use of the drug in the treatment of a series of cases of acute bacillary dysentery.

Considerable attention was again given to the mechanism of action of the sulfonamide group of drugs. J. T. Litchfield, Jr., H. J. White, and E. K. Marshall, Jr., from Johns Hopkins University reported that by determination of the median survival blood concentration for neoprontosil and sulfanilamide in mice infected with a B-hemolytic streptococcus they concluded that the entire chemotherapeutic activity of neoprontosil is due to the sulfanilamide formed from it in the animal organism.

The mechanism of action of sulfapyridine was studied by A. Dorfman, L. Rice, and S. A. Koser, of the University of Chicago. They found that the stimulation of respiration normally produced by the addition of nicotinamide to the culture medium of dysentery bacilli grown on a nicotinamide deficient synthetic medium is completely inhibited by the addition of sulfapyridine, acetylsulfapyridine, or sulfathiazole. This inhibition of respiration by sulfapyridine can be partially

potent principles in tincture of digitalis is absorbed from the gastrointestinal tract, the percentage varying for different specimens of leaf. Digitoxin-like preparations are practically completely absorbed after oral administration. Lanatoside C is absorbed much less rapidly and completely than is digitoxin. Experiments in man supported the statement of R. A. Hatcher and C. Eggleston that the gastrointestinal absorption of digitalis and its purified principles parallels that in the cat. The digitoxin-like materials which are almost completely absorbed in the cat, are also well absorbed in man since the intravenous and oral digitalizing doses are the same, about 3 cat units. About 20 cat units of digitalis orally are required to produce the same effect. Lanatoside C which is poorly absorbed in the cat is also poorly absorbed in human beings since the equivalent therapeutic doses of this glycoside are about 4 cat units intravenously and about 40 cat units orally.

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REPORT ON THE FIFTY-THIRD ANNUAL MEETING OF THE  
AMERICAN PHYSIOLOGICAL SOCIETY, CHICAGO, ILL.,  
APRIL 15-19, 1941\*

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*(From the Department of Surgery of the Medical School, University of Minnesota)*

THE following report covers a few of the many papers presented before the Society at the joint Session of the Federation.

C. H. Best and D. Y. Solandt, from the University of Toronto, Toronto, studied traumatic shock in a large number of dogs and concluded that fluid loss at and adjacent to the site of injury, as measured by a volume displacement technique, though usually a major factor was not the only etiologic agent responsible for death. Their own experiments, as well as those of Bayliss, Cannon, Moon, Essex, and collaborators, suggest the action of a toxic factor playing a role, after its release from injured tissue.

Micromanipulative studies, in the mesentery and tongue of the frog, on vascular responses to localized microinjury and to remote trauma by Robert Chambers and by Benjamin W. Zweifach, respectively, Washington Square College, New York City, suggest the evolution of a toxic substance. Following trauma there is a general loss of vascular tone characterized by dilatation of venules, enlargement of capillary bed and capillary stasis, an absence of rhythmic contractions in arterioles and their refractoriness to contractile nervous influences, along with a generalized increased permeability of vessel walls, as noted by increased diffusibility of certain dyes.

This sequence is consistent with the findings of M. L. Cullen, A. E. Schecter, and N. E. Freeman, of the School of Medicine, University of Pennsylvania, Philadelphia, that a reduced circulation of blood is present in the uninjured limb of ether anesthetized dogs during a state of traumatic shock. Hemococentration and elevation of serum specific gravity in their experience developed only after failure of circulation.

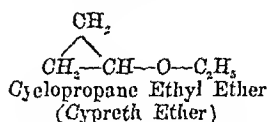
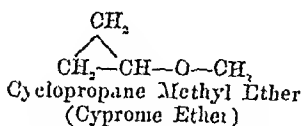
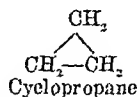
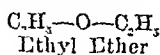
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\*Abstracts of all the papers submitted at this meeting will appear in the *American Journal of Physiology*.

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dose of morphine. The analgesia was produced more quickly and lasted for a longer period of time than when morphine was given alone. Atropine produced a slight decrease in the analgesic effect of morphine, while epinephrine not only decreased the analgesia but in some cases completely abolished it.

The synthesis of a new type of inhalation anesthetic was reported by J. C. Krantz, Jr., and S. E. Forman, of the University of Maryland. They reported the preparation and testing of two ethers of cyclopropane, thus combining the properties of both types of compounds.



Cypreth ether is a true hybrid molecule between ethyl ether and cyclopropane. Its potency in laboratory animals approximately equals that of chloroform and its anesthetic index is more than twice as great as that of ethyl ether. Cyprome ether has been employed in human anesthetics and is intermediate in characteristics between ethyl ether and cyclopropane.

A considerable number of papers were presented dealing with drugs acting on the heart and circulation. G. E. Fahr and J. S. LaDue, of the University of Minnesota, reported on the effects of intravenous administration of lanatoside C, a crystalline cardiac glycoside from *Digitalis lanata*. A dose of 16 mg. of lanatoside C was administered intravenously to ten patients with severe heart failure associated with normal sinus rhythm. Control teleoroentgenkymograms, blood pressure and circulation time measurements were made at the start of the experiment. All patients showed a prompt increase in the stroke volume of the heart. Optimal improvement was shown after 30 to 60 minutes, the transverse diameters of the hearts were 0.5 to 2.0 cm. smaller than at the beginning of the experiment, and the stroke output increased 10 to 40 per cent. In all cases except one there was a parallel increase in blood pressure and a decrease in circulation time.

Walter Modell and Harry Gold, of Cornell University, reported on the use of digitalis to prevent exaggerated acceleration of the heart during exercise in patients with auricular fibrillation. Gold had previously shown that digitalis action on the heart is made up principally of two factors, a vagal factor which is abolished by atropine, and an extravagal factor not affected by atropine. Ventricular rate is controlled by both factors, the extravagal factor assuming greatly increased prominence as complete digitalization to the point of minor toxic symptoms is approached. In their present study on eleven patients, Modell and Gold found that exercise to the limits of endurance failed to accelerate the ventricle appreciably above 100 a minute when "extravagal" digitalization was obtained, and that, therefore, contrary to the customary belief, the exaggerated acceleration of the heart during free physical exercise may be satisfactorily controlled by "extravagal," that is, complete digitalization in patients with auricular fibrillation.

In another paper Janet Travell and Harry Gold reported on the extent of absorption of some digitalis preparations from the gastrointestinal tract in the cat and man. In cats only a small proportion, usually about 25 per cent, of the



E. Cortell and E. Gellhorn, from the College of Medicine, University of Illinois, Chicago, called attention to the fundamental differences in the reactivity of the autonomic and the cerebrospinal nervous systems in cats. Whereas somatic movements elicited by direct central stimulation decline, the autonomic centers exhibit an increased excitability during anoxia. This is characterized by an increased response of the nictitating membrane, pulmotor phenomenon, and an elevation of blood pressure. Similar differences were found during hypercapnia and hypoglycemia. It is assumed that such characteristics of the autonomic system make possible the adjustment reactions to alterations of homeostasis.

J. G. Schnedorf and T. S. Orr from the University of Kansas School of Medicine, Kansas City, determined the effect of high concentrations of oxygen upon shock induced by trauma, histamine, and hemorrhage. In all instances under comparable conditions of blood loss, dogs treated with the inhalation of 100 per cent oxygen survived longer and maintained a higher blood pressure. In addition animals so treated were able to stand the loss of larger volumes of blood. One hundred per cent oxygen significantly increased the arteriovenous oxygen values.

That high concentrations of oxygen when inspired for prolonged periods of time may not have an unmixed blessing was inferred by John Randolph Paine, Ancel Keys, and David Lynn, from the University of Minnesota Medical School, Minneapolis. Dogs kept in a specially constructed chamber breathing oxygen at a concentration of 90 per cent or over invariably succumbed from cardiorespiratory failure in less than a week. With the higher concentrations this interval was materially shortened. Control animals respiring air survived without detectable deviation from normalcy. Autopsy findings of those dead from high concentrations of oxygen, usually showed evidence of pulmonary congestion with interstitial edema and polymorphonuclear cell infiltration, plus the signs of right heart failure.

Observations by P. S. Steinitz, E. S. Megibow, and L. N. Katz, of Michael Reese Hospital, Chicago, on the changes of dynamics following experimentally produced major and multiple minor pulmonary emboli suggest that the mechanism of death and the circulatory alterations are due to the development of an abrupt and persistent systolic and diastolic pulmonary hypertension, as recorded by the Hamilton manometer in anesthetized and unanesthetized trained dogs. The hypertension manifest in the lower circuit appears related to the amount of mechanical obstruction to its blood flow. Usually there is an elevation of respiratory rate, an increase in cyanosis, and elevation of systemic venous pressure, coincidental and progressive with the degree of pulmonary hypertension. The ultimate cause of death, with the exception of a few animals dying of ventricular fibrillation, in experimental pulmonary embolism, is failure rapidly or slowly of the right heart.

Investigations by Robert Dean and Maurice B. Visscher, from the University of Minnesota Medical School, Minneapolis, on the kinetics of lung ventilation using helium or nitrogen and oxygen mixtures point out that the clinical advantage of the former is founded on the ability of helium to resist turbulence of flow at rates up to three times the value for air. Turbulence in their experience occurs only in the trachea and larger bronchioles. Since the work required to maintain a turbulent flow is greater than for a similar rate of streamline flow, the substitution of helium-oxygen mixtures for air eases the respiratory efforts in cases of tracheal obstruction.

William H. Olson, F. Neuwelt, H. Gutmann, H. Neeheles, and S. O. Levinson, of Michael Reese Hospital, Chicago, noted regularly in anesthetized dogs following spontaneous traumatic or morphine shock an elevation of 100 to 300 per cent in the circulation time, using the cyanide method. This circulation time was effectively lowered by an infusion of saline solution, serum or plasma, with the duration of the change reflecting the efficacy of the fluid administered, i.e., following the intravenous saline solution the reduction of circulation time was brief, while after an infusion of serum or plasma a prolonged improvement of circulation time was noted.

Shock developing in barbital anesthetized dogs following repeated hemorrhages or acute plasmaphoresis and maintained thusly at a mean blood pressure of 40 to 70 mm Hg for two hours was found by Jacob M. Werle and Richard S. Cosby, of Western Reserve University Medical School, Cleveland, to be irreversible despite reintroduction of all the blood or plasma withdrawn. It was felt that the failure to respond did not represent visceral engorgement nor withdrawal of injected fluid by the spleen as determined by autopsy findings and measurements.

Henry N. Harkins, R. T. Boals, and C. Frank Chunn, of Henry Ford Hospital, Detroit, studied the fate of fluids injected into animals with traumatic shock and were in agreement with the idea postulated by Moon that there is a generalized increased capillary permeability. Whereas in normal animals there was an initial blood concentration following the intravenous injection of concentrated plasma, followed by a gradual return to normal values, animals in shock administered plasma concentrate developed a sudden transient dilution of the plasma, immediately superseded by a reconcentration in the severe cases. It was concluded that this represented a difference in capillary permeability between normals and animals in shock.

J. D. Beale, Jr., L. L. Chastain, and H. S. Heils, from the School of Medical Sciences, Wake Forest College, Wake Forest, N. C., pointed out that using barbital anesthetized dogs it was possible to elevate the arterial pressure as much as 64 mm Hg by placing the animal in a Trendelenburg position 70° from the horizontal. In instances of shock from hemorrhage or trauma, where the pressure was maintained below 70 mm. Hg for several hours, inversion resulted in the usual elevation of pressure unless vasomotor, respiratory, or cardiac failure had supervened to a severe degree. They felt that these terminal states could be relieved or postponed by keeping the animal in shock in the inverted posture.

Chemical changes were studied in dogs subjected to trauma until the carotid artery blood pressure reached 50 to 60 mm Hg by H. Gutmann, William H. Olson, H. H. Kroll, S. O. Levinson, and H. Neeheles, of Michael Reese Hospital, Chicago. A significant drop in arterial  $\text{CO}_2$  and  $\text{O}_2$  values, simultaneously with an elevation of lactic acid concentration and a decrease in pH, not explainable on the basis of the lactic acid accumulation alone, were recorded. Arteriovenous oxygen differences were marked. Hemoglobin and hematocrit readings were indicative of hemoconcentration, while the specific gravity of whole blood and plasma proteins varied inversely. The plasma potassium rose terminally and also transiently in instances of more severe traumatization.

J. F. Mannery and D. Y. Solandt, from the University of Toronto, Toronto, also noted an increase in serum potassium value in dogs traumatized to a shock level blood pressure. Despite restoration of blood pressure and circulation time (even temporarily) by an infusion of blood substitutes, the chemical changes were but partially reversed.

tachycardia in anesthetized dogs who had been thyroidectomized two to four weeks previous. There was a prolongation of the effect in animals fed desiccated thyroid gland to a state of hyperthyroidism.

H. S. Wigodsky and B. P. Phipps, of Northwestern University School of Medicine, Chicago, studied the ability of the gall bladder to eliminate sediment by placing sand in the canine gall bladder and noting the residuum radiographically while administering various diets. Ketocholel tablets, a cholagogue, were significantly inferior to a cream-and-eggs mixture in promoting cholecystic elimination of sand. Repeated evacuation, not choleresis per se, tends to flush the gall bladder.

H. A. Davenport and R. T. Bothe, of Northwestern University Medical School, Chicago, noted the reaction of living bone to several metals and alloys. Two-millimeter pegs of the following substances were so placed as to contact the periosteum, cortex, and medulla in aseptically drilled holes of the cat femur: Al, Ag, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Ti, W, Au-Pt, Mn-Ti, Cr-Mn, Fe-Ti, stainless steel, and vitallium. Two implants of dissimilar metals were usually made in each femur. Readings of electrical potential differences between couples of dissimilar metals failed to support the idea that electrolysis is the cause of an unfavorable bone reaction to an introduced foreign body.

Ti, Pb, Cr, Al, vitallium, and stainless steel were well tolerated. The authors concluded "that living bone reacts to adjacent metal in the manner conditioned by the solubility of the metal in body fluids, plus the effects (locally) of salts so formed."

Emphasis was lent to the acid factor in the genesis of duodenal ulcer formation by the work of **Richard L. Varco** and **C. F. Code**, from the University of Minnesota Medical School, Minneapolis. Following the daily intramuscular injection into dogs of a histamine in beeswax-mineral oil mixture, which calls forth a continuous, copious flow of highly acid gastric juice maintained for many hours, there developed single or multiple perforating duodenal ulcers in each of three animals tested.

**Lyle J. Hay**, **David Lynn**, and **Owen H. Wangenstein**, from the University of Minnesota Medical School, Minneapolis, confirmed these findings in a more extensive series of dogs and by applying this method to a variety of animals were able to produce gastric and/or duodenal ulcers in pigs, guinea pigs, rats, rabbits, woodchuck, chickens, ducks, calves, cats, and a monkey.

Prevention of the development of experimental gastrojejunal ulcers in Mann-Williamson dogs by the use of enterogastrone was reported by **A. P. Hands**, **G. B. Fauley**, **Harry Greengard**, and **A. C. Ivy**, from Northwestern University Medical School, Chicago. Enterogastrone in an amount known to abolish gastric tone and motility for sixty minutes and to halve the gastric secretory response of total pouch dogs was administered three times daily intravenously. At the end of eight to fourteen weeks all twelve test animals had exhibited no untoward reactions and had improved in general physical status without manifesting any symptoms of an ulcer. This period definitely exceeds the interval required for untreated Mann-Williamson dogs to exhibit characteristic symptoms of ulcer formation.

Senescence has no effect on the emptying time of the stomach after a standard meal, concluded **Edward Van Liere** and **David Northup**, of West Virginia University, Morgantown, on the basis of fluoroscopic study of twelve men, averaging 70.7 years of age, compared with a group of healthy medical students.

**Keith S. Grimson**, **Alf S. Alving**, and **Wright Adams**, from the University of Chicago, Chicago, reported the effect of total and subtotal sympathectomies on the blood pressure of hypertensive persons. In the former, with a three-stage procedure the entire thoracolumbar chains, splanchnic nerves, and celiac ganglion are removed; in the latter, a two-stage procedure, the sympathetic ganglia bilaterally below the first lumbar only are preserved. The procedure was limited to 11 patients with essential or idiopathic hypertension, 2 receiving all three stages, 7 two stages, and 2 bilateral lumbar sympathectomy and splanchnic nerve section. There was 1 death. Total sympathectomy was demonstrated to be compatible with the relatively normal existence, where gastrointestinal, urinary, and respiratory functions remain fairly unaltered. Blood pressure values fell to approximately normal values in 4 of the 9 hypertensives subjected to total or subtotal sympathectomies; 3 other patients had a definite lowering of blood pressure postoperatively. The group has been observed two to ten months and in some there is a tendency to a gradual elevation of blood pressure. Bilateral lumbar sympathectomy and splanchnic nerve section effected but a slight alteration of the blood pressure.

Cyclopropane augments the adrenalin effect on the autonomic tissues of the dog's heart, stated **J. W. Stutzman**, of the University of Wisconsin Medical School, Madison. Whereas in the unanesthetized animal 0.01 mg. of adrenalin per kilogram produces only escape phenomena, under anesthesia it usually induces multifocal ventricular tachycardia. In studies on the influence of thyroid on cyclopropane-adrenalin tachycardia, he noted a shortening of the adrenalin

every opportunity should be taken to strengthen the desire to maintain it." It is also undoubtedly true that in any time it is profitable for students of medical science to study carefully the great classics of its literature, of which Harvey's *De Motu Cordis* is without question one of the greatest, and, perhaps, in the light of its time, the greatest of all.

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**Office Urology** (With a Section on Cystoscopy). By P. S. Pelouze, Philadelphia, 1940, pp. 766, with 424 illustrations. W. B. Saunders Company. \$10.00.

This work is a good deal more comprehensive than is indicated by its title. Containing, as it does, helpful suggestions as to nonsurgical therapy and diagnosis, it is sure to be especially valuable in general practice and to be of use to anyone who treats urological patients.

Included are sections on the arrangement of the office, on anatomy and physiology, on the various diagnostic maneuvers, and on all of the diseases of the urogenital tract commonly seen and susceptible of treatment in the office. The section on cystoscopy is informative and comprehensive. One cannot but be impressed by the author's sensible views upon such controversial subjects as the endocrines and sexual problems. He is entirely free from the overenthusiasm and superstitions so often exhibited by physicians who dabble in these fields.

Obviously, no urologist can read a book written by another without finding something to criticize; this one is no exception. The relative lack of references to the literature is undesirable. Some of the most useful information is a little obscured by cumbersome phraseology, and the author's tendency to invent words is at times confusing. It is regrettable that he has tried to perpetuate two of urology's hoariest myths; namely, that sudden emptying of the distended bladder is dangerous, and that procaine is an anesthetic when applied topically. It is not clear exactly why he omits the sulfonanilides in the treatment of gonorrhea confined to the anterior urethra of the private patient while employing it in the clinic patient. In the opinion of the reviewer, the author's doubts about the possible success of urethroplasty in hypospadias are not justified, and the injection treatment of hydrocele is a little more useful than one would suspect from his book. Many of the illustrations would be greatly improved by the substitution of good photographs for some rather poor drawings of pathologic specimens.

Nevertheless, this book ought to be read by those at whom it is aimed.

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**Surgical Anatomy of the Head and Neck.** By John Finch Barnhill, M.D., F.A.C.S. Ed. 2. Pp. 773, with 431 illustrations. Baltimore, 1940, The Williams & Wilkins Co. \$15.

This book, a second edition, which is obviously more or less a reproduction of a series of lectures given in postgraduate course for otolaryngologists, is another applied anatomy of the head and neck.

It contains a running description of the anatomy of these parts suitable, no doubt, for the purpose of these lectures. The illustrations, mostly drawn by the author himself, demonstrate remarkable talent, but should have been redrawn by a professional artist for publication. They are mostly labeled with numbers, the key for which is given in the legend below the figure. It would be much less laborious

## Book Reviews

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**Diagnosis and Treatment of Menstrual Disorders and Sterility.** By Charles Mazer and S. Leon Israel. Pp. 485, with 108 illustrations. New York City, 1941, Paul B. Hoeber, Inc. \$6.50.

This practical volume summarizes the accepted methods for diagnosis and treatment of the gynecologic conditions about which it is written. History and theory have been omitted, and it is purely clinical, having been designed primarily for the family physician, so that pertinent information is readily available to him.

Unfortunately, the authors adhere to the older use of the term anovulatory menstruation instead of anovulatory bleeding; otherwise the terminology is accurate throughout. Each term employed is clearly defined, immediately familiarizing the reader with the condition to be discussed. "Irregular shedding" of the endometrium is not treated here as a separate entity but is merely mentioned by quotation from some of its most ardent advocates.

The sound recommendations for diagnosis and treatment suggest complete and careful patient study. Particularly gratifying is it to see this volume, which will find wide usage, advocate the routine use of diagnostic curettage even in the presence of pathology which might be responsible for the uterine bleeding. One of the specific recommendations for its use is in the patient with known myomata uteri in whom the bleeding may be the result of a submucous myoma, but the myomas might, on the other hand, be innocently associated with a malignancy of the body of the uterus. It is the repetition of such basic principles which will help avoid the disasters that are bound to follow when the physician uses radium or x-ray or resorts to hysterectomy without taking time to make a positive diagnosis by methods which are available to all.

Of particular usefulness in everyday practice is the appendix, which lists all the commercially available standardized endocrine products and their dosages. The text is helpful in this, since frequently the dosages are given in terms of different units. The biologic units are all defined, making this book as complete in every detail as is possible with relative brevity.

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**Anatomical Studies on the Motion of the Heart and Blood.** By William Harvey, translated with annotations by Chauncey D. Leake. Pp. 150, with 9 illustrations. Springfield, Ill., 1941, Charles C Thomas, Publisher. \$1.50.

A third edition of the Leake translation of the Harvey classic is proof that interest in the roots of modern physiology and experimental medicine is not dead. This volume, like its predecessors, is handsomely printed on excellent paper. It carries the more important facsimile illustrations from Harvey's original work.

The translator justifies the presentation of a new edition at this time in the preface, which begins: "In spite of the acute impact of political and economic events, the less tangible cultural relations between countries may be more significant in the long run. . . . With today's threat to the achievement of our cultural ideal,

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## Original Communications

### THE BACTERIOLOGY OF PEPTIC ULCERS AND GASTRIC MALIGNANCIES: POSSIBLE BEARING ON COMPLICA- TIONS FOLLOWING GASTRIC SURGERY

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#### INTRODUCTION

**S**URGEONS have always been aware of the danger of peritonitis following operations upon the stomach and duodenum. Freidrich and Weber<sup>17</sup> in a review of 207 subtotal gastrectomies for carcinoma reported a mortality of 25.1 per cent in which peritonitis was the cause of death in 70 per cent of these fatal cases. In resections for gastric ulcer 50 per cent of the deaths were due to peritonitis; whereas, in their duodenal ulcer cases only 20 per cent of the deaths were due to peritonitis. In spite of the fact that the operation of subtotal gastrectomy may have been performed with meticulous technique and that the intestinal sutures were carefully done, leaks along the suture line occasionally developed. These cannot always be ascribed to errors in technique. It was thought that some of the postoperative complications of this nature may be ascribed to the bacteriologic flora of the stomach and duodenum. Accordingly, an effort was made to make bacteriologic studies of the gastric and duodenal flora and peritoneal fluids during the operation and at various times thereafter.

The literature on the bacteriology of the stomach and duodenum in health and disease is voluminous. Cultures have been obtained (of gastric contents) by aspiration and from scraping and sectioning ulcers and carcinomas either at the operating table or post-mortem examinations. Numerous microorganisms have been recorded; namely,

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to follow if directly labeled at the end of the leads, where space permitted. There is a certain superficiality about the book which is in contrast to the didactic style in which it is written. Some discussions of physiology and pathology are particularly noticeable in this respect.

Some of the book was obsolete when published. The index is incomplete.

**Diagnosis and Treatment of Arthritis and Allied Disorders.** By H. M. Margolis, Pp. 551, with 140 illustrations. New York, N. Y., 1941. Paul B. Hoeber, Inc. \$7.50

The author has covered a wide field of material relative to rheumatoid and joint diseases. There is a good bibliography covering many phases of the subjects reviewed. A number of the author's conclusions relative to etiology and therapy are controversial, as would be expected of any work covering rheumatoid disease at this time. The chapter relative to the recognition and correction of arthritic deformities is of special interest and well illustrated. Perhaps of greatest interest, however, are the chapters dealing in some detail with shoulder, low back, and sciatic pain, conditions that often represent difficult problems in diagnosis and management.

**The 1940 Year Book of Pathology and Immunology.** Edited by Howard T. Karsner, Professor of Pathology, Director of the Institute of Pathology, Western Reserve University, Cleveland (Pathology), Sanford B. Hooker, Professor of Immunology, Boston University School of Medicine (Immunology). Pp. 868, with 115 illustrations. Chicago, 1940, Year Book Publishers, Inc. \$3

This is a new addition to the series of Year Books. The subjects embrace two fields of vital importance in modern medicine. Both editors are well known in their respective fields.

Dr. Karsner has made a comprehensive selection of the literature on pathology for the past year or two. One interesting and stimulating feature is the response of well known investigators to summarize their contributions rather than an attempt on the part of the editor to abstract their many papers. Thus there is a review of "Familial Tumors of the Rabbit," by Greene, "Intercellular Lipoid Protoplasmic Reactions," by Hass, "Experimental Hypertension," by Kahn, "Frog Carcinoma," by Lucke, and "Nephrotoxic Nephritis," by Smadel. Consideration is also given to the pathology of tumors and the different systems, with a final chapter on technical notes.

The last half of the book is devoted to immunology, which should prove to be definitely useful to the pathologist and immunologist. Dr. Hooker has reviewed the immunological advancements pertaining to bacterial diseases, viral and rickettsial diseases, diseases due to protozoa, fungi, and higher parasites, and tumors. The rapid advancements in immunology are reflected in the section in immunochemistry. An attempt has been made to review the recent literature pertaining to therapy with the sulfonamide compounds, and an inadequate presentation has resulted because one can hardly do justice to the subject by abstracting only eleven original papers.

Both authors have increased the value of this volume by their editorial comments. The book is recommended for anyone who seeks a concise and authoritative review of recent developments in pathology and immunology.



tomy are included in this series so that although the bacterial flora was carefully and completely studied, it is of little significance in our problem.

In order to investigate the possible relationship of the bacteriology of the stomach and duodenum to postoperative infections, cultures were made from all specimens removed by subtotal gastrectomy. In many cases throat cultures and postoperative stomach cultures (obtained through a Levine tube) were also made. The cases were observed after operation for evidences of wound infections, intraperitoneal complications, peritonitis, and pulmonary complications.

#### METHODS

The specimens obtained by subtotal gastrectomy were received into a sterile basin from the operating table. With sterile instruments and gloves small sections of the serosa and mucosa were removed and placed in plain broth. A section was made of lymph glands if they were present, and when no nodes were palpated, a small segment of perigastric fat was excised for culture. If contamination of the serosa occurred during the operative procedure, only a specimen of mucosa was obtained. Sections were taken from either the ulcer bases or carcinoma lesions. When no ulcer was present in the resected surgical specimen (many ulcers adherent to or penetrating into the pancreas were left in situ), the mucosa immediately adjacent to the ulcer was used. Thus, in most instances the culture represented the bacteria present in the actual pathologic lesion. The specimens were then triturated without delay in the broth in which they were suspended and seeded into 1 per cent glucose broth, cooked liver broth under a vaseline seal, plain agar, ascitic fluid agar, blood agar and endo medium plates, and broth containing 1 per cent esculin (for the identification of enterococcus). All anaerobes were transplanted to fresh blood agar plates and cultured in anaerobic jars containing hydrogen for forty-eight to ninety-six hours.

Anaerobiosis was obtained in a tightly sealed jar from which the air was in part removed by a vacuum pump and subsequently the remainder of the air replaced by hydrogen under pressure in the presence of the catalytic agent, palladinized asbestos.<sup>26, 27</sup> The indicator for anaerobiosis was 0.1 c.c. of 1 per cent aqueous methylene blue in 10 c.c. of glucose broth which became colorless under anaerobic conditions. Various mediums used included Smith-Noguchi, Hiss serum sugar media (dextrose, mannite, maltose, lactose, saccharose), gelatin, litmus milk, and ascitic fluid agar. Surface and shake cultures were employed. Identification depended on staining characteristics, type of growth, fermentation of sugars, acid production, liquefaction of gelatin, coagulation of litmus milk, agglutination by specific sera, and tests for animal pathogenicity.

diplostreptococcus,<sup>1</sup> observed on spreads only, streptococci<sup>2</sup> of undetermined type, gram-positive diplococci<sup>3, 4</sup> as observed on spreads only, *Streptococcus viridans*,<sup>5-7</sup> enterococcus,<sup>6, 9, 17A</sup> *Staphylococcus albus* and *Staph. aureus*,<sup>6</sup> *Bacillus coli*,<sup>6, 10, 13</sup> *B. subtilis*,<sup>8</sup> *B. proteus*,<sup>8</sup> diphtheroids,<sup>8</sup> torula,<sup>11</sup> and gram-negative bacilli,<sup>13</sup> as observed on spreads. Various authors also have reported on the percentage of sterile cultures obtained. Appelmans and Vassiliadis<sup>6</sup> found sterile cultures in 10 out of 23 duodenal ulcer cases, 3 out of 17 gastric ulcer cases, and positive cultures in all gastric carcinomas. Their cultures were all obtained either from resected specimens by scraping the lesion with a platinum loop or from stomach contents. Streptococci were recovered by Rosenow<sup>7</sup> in 42 out of 54 cases of gastric ulcers (resected specimens). In 82 per cent of gastric ulcer cases and 92 per cent of duodenal ulcer cases Löhr<sup>14</sup> found the stomach or duodenal contents either to be sterile or to contain nonpathogenic organisms. However, he reported that 72 per cent of the gastric carcinomas yielded positive cultures, many of which were due to *B. coli*. Hewetson<sup>11</sup> in 1904 described a series of cultures of the stomach and jejunum taken at operation. Eighteen out of 36 stomach cultures and 16 out of 29 jejunal cultures were sterile. From this work Hewetson concluded that peritonitis following operations on the stomach and jejunum was caused by bacteria other than those present in these organs. This view has not been supported by the subsequent work of numerous authors. In 11 cases (4 gastric ulcers, 4 duodenal ulcers, 3 jejunal ulcers) Moutier<sup>4</sup> found the presence of *Str. viridans* in 10 instances. The relationship of gastric juice and hydrochloric acid upon the growth of microorganisms in vitro has also been exhaustively investigated. In his textbook Rehnss,<sup>8</sup> quoting the work of Bartle and Harkins, includes a table listing the microorganisms compatible with various acid figures. Staphylococci are more resistant to hydrochloric acid than *B. coli* which in turn are more resistant than streptococci (type of streptococcus not mentioned in text).

It is evident from this review of previous investigators that there are no specific groups of microorganisms responsible for postoperative infections. The microorganisms have not always been completely identified.<sup>1-4</sup> In many instances the only descriptive terms employed were "gram-positive cocci," "tetrads," etc. If the cultures were obtained through a stomach tube, there was always the possibility of contamination with bacterial inhabitants of the mouth. In some studies only the spreads were examined without any attempt to culture the flora.<sup>1-3</sup> Meleney and associates<sup>18</sup> in a review of 106 cases of peritonitis (76 appendiceal, 10 related to small intestine, 6 to gall bladder, 6 to colon, and 8 miscellaneous) reported *B. coli* in 87 per cent, *Streptococcus viridans* in 49 per cent, and *B. welchii* in 38 per cent of the positive peritoneal cultures. No cases of peritonitis following subtotal gastrec-

TABLE I  
MICROORGANISMS CULTURED FROM MUROSA, SEROSA, NODE, AND FAT IN VARIOUS TYPES OF LESIONS (85 CASES)  
ACID FIGURES AT HEAD OF COLUMN

Gram-negative rods were further identified by fermentation reactions of mannite, maltose, dextrose, saccharose, and lactose, by the indol reaction, and finally by agglutination tests. Gram-positive bacilli producing fermentation, acid, and abundant gas in anaerobic cultures containing sugars were identified as *B. welchii* (*Cl. perfringens*) by typical morphology, liver damage,<sup>28</sup> positive rabbit-liver test,<sup>28</sup> gelatin liquefaction without lysis of coagulated protein<sup>29</sup> and well-pronounced capsule formation. *Staph. aureus* and *Staph. albus* were classified as A (pathogenic) or B (nonpathogenic) by the mannite fermentation, hemolysis on blood plates, and coagulase tests.<sup>25</sup> All streptococci were classified as either viridans (alpha), hemolytic (beta), or anhemolytic (gamma) (Brown<sup>24</sup>). Streptococci of the hemolytic variety were further grouped by precipitation reactions of the crude carbohydrate extracts with specific antisera (Lancefield<sup>23</sup>) and by their fibrinolysis of human fibrin described by Tillett.<sup>22</sup> All strains of *Str. hemolyticus* recorded in Tables I and VI were fibrinolytic and belonged to the Lancefield Type A pathogenic for man.

Acid titrations were made upon the stomach contents following a Rehfuess test meal and recorded in units of free and total acid. If no free acid was present, histamine was always administered subcutaneously.

## RESULTS

A great variety of microorganisms were cultured from the specimens. These presumably pathogenic microorganisms listed in order of their frequency are *Str. viridans*, *Str. hemolyticus*, *Str. anhemolyticus*, *B. coli*, *B. welchii*. In addition, there were encountered diphtheroids, *Micrococcus catarrhalis*, and enterococcus, which are of rather doubtful pathogenicity; and also clearly saprophytic microorganisms as *B. subtilis*, yeasts, *Staph. aureus* and *Staph. albus* of B type.<sup>25</sup>

As may be seen from Table I, positive cultures were obtained in 93.7 per cent of gastric malignancies, 83.3 per cent of the gastric ulcers, 36.6 per cent of duodenal ulcers, and 37.9 per cent of secondary or complicated peptic ulcers. Presumably pathogenic microorganisms were recovered in 88 per cent of the malignancies and 30 per cent of the benign ulcer cases (as a group). In 24 cases in which the lymph nodes were cultured, 25 per cent were found to contain pathogenic microorganisms (71 per cent sterile) (Table I). Specimens of the serosa yielded pathogenic cultures in 15 per cent of 54 cases (37 were sterile) (Table I). Cultures of the perigastric fat (16 cases) were sterile in 11 and contained pathogenic microorganisms in 5 cases (31 per cent) (Table I). If contamination occurred in these 5 cases, it is important since it indicates contamination during the surgical procedure which then is a warning to the operator.

TABLE I  
MICROORGANISMS CULTURED FROM MUCOSA, SEROSA, NODE, AND FAT IN VARIOUS TYPES OF LESIONS (85 CASES)  
ACID FIGURES AT HEAD OF COLUMN

MICROORGANISM	GASTRIC ULCERS (6) AVERAGE FREE ACID UNITS, 58+ PATHOGENS, 50%					DUODENAL ULCERS AND EROSION (18) ULCER LEFT IN (12) AVERAGE FREE ACID UNITS, 64+ PATHOGENS, 17%					GASTRIC MALIGN- NANCIES (16) AVERAGE FREE ACID UNITS, 18- PATHOGENS, 88%					SECONDARY ULCER, BLEED- ING ULCER, ETC. (29) AVERAGE FREE ACID UNITS, 58+ PATHOGENS, 31%					PREOPERATIVE SULFANILAMIDE (4)				TOTAL
	MUCOSA		SEROSA		FAT	MUCOSA		SEROSA		FAT	MUCOSA		SEROSA		FAT	MUCOSA		SEROSA		FAT	MUCOSA		SEROSA		
	ULCER	NO ULCER	ULCER	NO ULCER		ULCER	NO ULCER	ULCER	NO ULCER		ULCER	NO ULCER	ULCER	NO ULCER		ULCER	NO ULCER	ULCER	NO ULCER		ULCER	NO ULCER			
<i>Str. viridans</i>	2	1				1	1				10	2	4	1	1	1	1	1	1		1				22
<i>Str. hemolyticus</i>			1								4	1	3	1	1	1	1	1	1						14
<i>Str. anihemolyticus</i>											3	1	1	1											10
<i>Escherichia coli</i>											6	1				1									8
<i>Clostridium per- fringens</i>											3	1				1	1	1							8
<i>B. friedlanderii</i>											1														1
<i>Staph. albus (A)</i>											3	1													7
<i>Staph. aureus (A)</i>											1					1	1								4
<i>Enterococcus</i>											1														1
<i>Staph. albus (B)</i>	1					3	2	4		1	3					2	2	2			1				21
<i>Staph. aureus (B)</i>						1	1											1			1				5
<i>Corynebacterium hodgkinii</i>	1					4		2		1	2					2	1			1					14
<i>Saccharomyces</i>						1					1					1	1			1					6
<i>B. subtilis</i>	1					2				1	2	1				1	1								8
<i>Neisseria catar- rhalis</i>																1		1							2
Sterile	1					6	5	16	5	3	1	9				7	4	11	3		2	1	1		

TABLE II

STOMACH CULTURES TAKEN BY LEVINE TUBE AFTER OPERATION (62 CASES)

<i>B. coli</i>	46
<i>Enterococcus</i>	29
<i>B. friedländeri</i>	5
<i>Str. hemolyticus</i>	4
<i>Str. anhemolytic</i>	3
<i>Str. viridans</i>	2
<i>B. welchii</i>	4
<i>Staph. aureus (A)</i>	4
<i>Staph. aureus (B)</i>	2
<i>Staph. albus (A)</i>	1
<i>Staph. albus (B)</i>	6
<i>B. proteus</i>	3
<i>B. pyocyaneus</i>	3
<i>B. subtilis</i>	3
<i>Neisseria catarrhalis</i>	2
<i>Corynebacterium hodgkinii</i>	1
<i>Saccharomyces</i>	1

Cultures of the stomach contents obtained by Levine tubes within twenty-four hours after subtotal gastrectomy were made in 62 cases and are summarized in Table II. *B. coli* was cultured forty-six times and enterococcus twenty-nine times in addition to a great variety of other microorganisms. No cultures were sterile. It may be stated, therefore, that following subtotal gastrectomy, the flora of the stomach closely resembled that of the intestinal tract below the duodenum regardless of the type of lesion encountered or the preoperative acid figures. Thus one may deduce that a free exchange of bacteria occurs at the gastro-enterostomy stoma.

Throat and stomach cultures with particular reference to *Str. hemolyticus* were performed in 41 patients. These cultures were taken over a period of two years. Positive throat cultures were obtained each month as follows: Jan. 2, Feb. 3, March 2, April 3, June 1, Oct. 2, Nov. 1, and Dec. 1. In only 3 cases (7.3 per cent) was there found *Str. hemolyticus* in the throat and stomach of the same individual. On the other hand, 12 patients had *Str. hemolyticus* in the throat and no hemolytic streptococci in the stomach. In this series the presence of hemolytic streptococci in the throat apparently had no significant bearing to the incidence of complications.

Table I shows the relation between free acid figures obtained by Rehfuess test meal and the percentage of significant cultures present. The outstanding fact is the high percentage (88 per cent) of presumably pathogenic microorganisms present in the carcinoma cases in which the acid figures are extremely low. In the simple and complicated ulcers the acid figures were very similar, but the percentage of significant positive cultures varied from 17 per cent in the simple duodenal ulcers to 50 per cent in simple gastric ulcers. One must assume, therefore, that the actual amount of free acid present in the stomach is not an important determining factor which controls the bacterial flora of the

gastric and duodenal lesions. Horsley,<sup>20</sup> Lahey,<sup>21</sup> and others have suggested preoperative lavage and instillation of weak hydrochloric acid solution in carcinoma cases in an effort to sterilize the stomach. The bacteriologic studies herein reported support the view that carcinoma cases have a very high percentage of positive cultures (93 per cent). Further study using our method of taking cultures of operative specimens as already described under Methods is necessary to state accurately whether there would be a decrease in the number of microorganisms and postoperative infections with their routine.

An attempt was then made to correlate these operative bacteriologic findings with the postoperative course of the patients. The possible relationship between the type of microorganisms and the postoperative complications is made in Table III. The observations seem to show

TABLE III  
MICROORGANISMS AND CLINICAL COURSE CORRELATED

MICROORGANISMS CULTURED AT OP- ERATION IN CASES DEVELOPING COMPLICATIONS	NUMBER OF COMPLICATIONS THAT DEVELOPED				MORTALITY (15) INCIDENCE	
	WOUND INFECTIONS (12) INCIDENCE	PULMONARY COMPLICATIONS (16) INCIDENCE	ABDOMINAL COMPLICATIONS (16) INCIDENCE			
<i>Str. viridans</i>	5 5/22	2 2/22	2 2/22		7	7/22
<i>Cl. perfringens</i> ( <i>B. welchii</i> )	3 3/ 8	2 2/ 8	3 3/ 8		3	3/ 8
<i>Str. hemolyticus</i>	2 2/14	1 1/14	2 2/14		3	3/14
<i>E. coli</i>	3 3/ 8	2 2/ 8	3 3/ 8		1	1/ 8
<i>Str. nonhemolytic</i>	2 2/10	1 1/10	3 3/10		0	
<i>Staph. albus</i> (A)	0	2 2/ 7	0		0	
<i>Staph. aureus</i> (A)	0	0	0		1	1/ 4
<i>Enterococcus</i>	0	0	0		1	1/ 1
<i>B. friedländeri</i>	0	0	0		0	
<i>Staph. albus</i> (B)	1 1/21	1 1/21	1 1/21		1	1/21
<i>B. subtilis</i>	1 1/ 8	1 1/ 8	1 1/ 8		0	
<i>Staph. aureus</i> (B)	0	0	0		0	
<i>Corynebacterium</i> <i>hodgkinii</i>	0	1 1/14	0		0	
<i>Saccharomyces</i>	0	1 1/ 6	0		1	1/ 6
<i>Neisseria catar-</i> <i>rhalis</i>	0	0	0		0	
Sterile	1	4	1		3	

that there was a greater incidence of wound and intra-abdominal infections in those cases in which positive cultures were obtained at operation. The presence of *Str. viridans*, *B. welchii*, *Str. hemolyticus*, *B. coli*, and *Str. nonhemolyticus* (i.e., indifferent gamma of Brown) alone or in combination were particularly significant. Considering the individual complications, the microorganisms listed above were present alone or in combination in 9 out of 12 patients (75 per cent) with wound infections, 12 out of 16 patients (75 per cent) with intra-abdominal complications, 10 out of 15 (66⅔ per cent) of the deceased patients, and in only 6 out of 16 patients (37.5 per cent) with pulmonary complications.

TABLE IV

PREDOMINANT MICROORGANISMS PRESENT IN WOUND INFECTIONS  
(CULTURES IN 8 CASES)

<i>Staph. aureus</i> (4)	2
<i>B. welchii</i> , <i>B. coli</i>	3
<i>Enterococcus</i> , <i>B. coli</i>	1
<i>B. welchii</i> , <i>Str. hemolyticus</i>	1
<i>B. proteus</i>	1

In Table IV are listed the important microorganisms cultured from wounds in 8 cases which developed wound infections (4 wound infections not cultured). In 3 of these 8 the similarity between the stomach and wound cultures was either partial or complete. One wound infection showed *Str. hemolyticus* and in this case neither the stomach nor throat contained this microorganism.

However, even without close correlation of the bacteriology in wound infections in these cases, one may assume that the presence of these microorganisms in the stomach and duodenum predisposes to postoperative complications related to the operative site (duodenal leak, peritonitis, and wound infections).

In an analysis of the 15 fatal cases (Table V) 8 deaths (53 per cent) could be ascribed to intraperitoneal infections (5 proved by post-mortem, 2 by abdominal puncture, and 1, clinically). Of the remaining 7 patients, 1 died of bronchopneumonia; 1 of functional obstruction; and the cause of death was not definitely determined in 5 patients upon whom no post-mortem examination was performed. In the 8 patients succumbing to peritonitis, the following microorganisms were cultured from the operative specimens: *B. welchii* (3 times), *Str. hemolyticus* (4 times), *Str. viridans* (5 times), which seemed then of importance in consideration of postoperative mortality from peritonitis. It is also of interest to note that in 5 deceased patients in whom death could not be definitely ascribed to peritonitis, *B. welchii* was present in cultures other than those taken of specimens at operation (one obtained by abdominal puncture postoperatively, one at post-mortem, one by stomach tube postoperatively, and two in wound infections).

In our series one is impressed by the fact that in the 7 cases in which *B. welchii* was cultured, morbidity and mortality rates were higher. Every patient in whom *B. welchii* was recovered at operation either developed some serious complication or died. It seems reasonable, therefore, to assume that if this microorganism is present, potential danger exists and may be of significant prognostic value. Following subtotal gastrectomy there is always a certain amount of devitalized tissue upon which these anaerobic organisms thrive. As a result, a dehiscence either of the duodenal closure or the enterostomy suture line occurred in 5 cases with subsequent leak (1 case) and localized peritonitis with subphrenic abscess (1 case) or generalized peritonitis and death (3 cases). As has



TABLE V  
ANALYSIS OF ALL DECEASED CASES

LESION	CAUSE OF DEATH	CULTURES AND REMARKS
1. Lymphosarcoma*†	Peritonitis; dehiscence of all suture lines	<i>B. welchii</i> , <i>Str. hemolyticus</i> , <i>Str. viridans</i>
2. Infiltrating adenocarcinoma with nodes*†	Peritonitis; bronchopneumonia	<i>Str. hemolyticus</i> , <i>Str. viridans</i> , ( <i>B. welchii</i> , <i>B. coli</i> at post-mortem)
3. Infiltrating scirrhus; adenocarcinoma with nodes†	Peritonitis clinically; no post-mortem	<i>Str. hemolyticus</i> , <i>Str. viridans</i> ( <i>B. welchii</i> , Levine tube postoperatively)
4. Infiltrating adenocarcinoma	Cause (?); no post-mortem	<i>B. coli</i> , enterococcus
5. Adenocarcinoma*†	Peritonitis; ( <i>B. welchii</i> invasion of jejunum, dehiscence of duodenal stump)	<i>Str. viridans</i> (premortem abdominal aspiration <i>B. welchii</i> )
6. Secondary gastrectomy for jejunal ulcer†	Peritonitis (no post-mortem) (abdominal culture at death revealed pus)	<i>B. welchii</i> , <i>Str. viridans</i>
7. Secondary gastrectomy (chronic duodenitis); no ulcer on specimen	Cardiac (?); second day after operation; no post-mortem	Sterile at operation
8. Bleeding duodenal ulcer (chronic gastritis, ulcer left in)*†	Peritonitis (duodenal leak) ( <i>B. coli</i> and enterococcus at post-mortem)	Yeast ( <i>B. welchii</i> in wound)
9. Secondary gastrectomy for chronic gastric ulcer	Rheumatic cardiac (?) (died third day; no post-mortem)	<i>Str. hemolyticus</i> , <i>Str. viridans</i>
10. Bleeding ulcer	Hemorrhagic bronchopneumonia; abdomen clean, sutures intact	<i>Staph. albus</i> (B)
11. Secondary gastrectomy*†	Peritonitis; dehiscence of duodenal stump	<i>B. welchii</i> ; post-mortem <i>B. welchii</i> and <i>B. coli</i>
12. Gastrectomy (secondary) and enterostomy	Functional obstruction with vomiting, alkalosis, etc.	Sterile ( <i>B. welchii</i> , <i>B. coli</i> in wound)
13. Chronic peptic ulcer	Pneumonia; peritonitis(?); no post-mortem	Sterile
14. Chronic duodenal ulcer†	Metastatic <i>Str. hemolyticus</i> peritonitis (from throat); no post-mortem	<i>Staph. aureus</i> (A)
15. Polypoid carcinoma with nodes	Died second day postoperative; shock; temperature, 106.8° F.; abdomen seaphoid; no post-mortem	<i>Str. viridans</i> and <i>Corynebacterium hodgkinii</i>

\*Proved by post-mortem examination.

†Death ascribed to peritonitis.

already been stated in the introduction, a great number of microorganisms have been reported as being cultured from the stomach and duodenum, but *B. welchii* has not been previously recorded to our knowledge. Freidrich and Weber,<sup>17</sup> for example, reported cultures on 25 gastric cases in which no anaerobes were recovered.

We feel that the finding of *B. welchii* in the cases herein reported was unexpected and of real clinical significance when found.

#### DISCUSSION AND CONCLUSIONS

The bacteriologic studies reported suggest several precautions and therapeutic innovations in operations on the stomach and duodenum in an effort to avoid postoperative morbidity and mortality.

1. Contamination of the peritoneal cavity and abdominal wall by gastric and duodenal contents should be avoided in view of the possible infectivity of these contents (93 per cent of the gastric malignancies, 83 per cent of the gastric ulcers, etc., showed positive cultures from the lesions which are in turn bathed by intraluminal fluids).

2. Inasmuch as 25 per cent of the nodes may contain microorganisms of presumable pathogenicity, one should treat the nodes and material contained in them as potentially infective.

3. Drainage of the peritoneal cavity down to the duodenal stump (to allow avenue of escape if leak occurs) or site of gross contamination by means of a lateral stab drain seems advisable, especially when there is some doubt as to the reliability of the suture lines. Whether the duodenal ulcer is completely excised or left in situ (*äuschaaltung*), the line of stomach resection, if feasible, should be made far enough away from the actual ulcer. This should be done because these tissues are less infected and healing is therefore better. The digestive action of pancreatic ferments, undue tension, and interference with blood supply are certainly important factors which contribute to the reliability or lack of security of the duodenal stump closure. The presence of pathogenic bacteria at or near the suture line may be another factor.

4. Since 93 per cent of the gastric malignancies had positive cultures, an "aseptic" method of resection similar to that used in colonic resection may be of advantage in gastric carcinoma cases. The Petz<sup>30</sup> or similar apparatus may solve this problem.

5. In view of possible *B. welchii* infection in a certain number of cases, tension at suture lines or strangulation of tissue may prove dangerous (7 of 85 cases had *B. welchii* present which organism thrives on dead tissue). The use of *B. welchii* antitoxin sera prophylactically and therapeutically in gastric cases is being seriously considered provided, of course, sera of sufficient potency may be secured.

6. In view of previous experience with sulfanilamide as a preventive measure against peritonitis in colon surgery,<sup>19</sup> this drug now is being

administered to a series of gastric cases before operation. Since sulfanilamide is effective against the *Str. hemolyticus* and has also been used with some success both clinically<sup>31, 32</sup> and experimentally<sup>31, 33, 34</sup> against *B. welchii*, it may prove of real value, particularly in the carcinoma cases which are heavily infected with both of these pathogens.

#### SUMMARY

1. Pathogenic microorganisms are frequently present in gastric and duodenal lesions (88 per cent of the malignancies, 30 per cent of the benign ulcers).
2. Postoperative complications and mortality rates appeared higher in cases with pathogenic microorganisms (streptococci of all varieties, *B. welchii*, *B. coli*, alone or in combination).
3. *B. welchii* indicate a grave prognosis when cultured from the stomach and duodenum at operation.
4. Low gastric acidity and a high percentage (88 per cent) of pathogenic microorganisms in carcinoma cases are noteworthy.
5. Cultures of the stomach after subtotal gastrectomy show intestinal microorganisms.

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## LEIOMYOMA MALIGNUM OF THE STOMACH

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NEOPLASMS of the smooth muscle of the stomach may be classified as: (1) benign leiomyoma, (2) leiomyoma malignum, (3) metastasizing leiomyoma, and (4) leiomyosarcoma. It is our purpose in this paper to report a gastric leiomyoma which had characteristics that stamped it as malignant and whose picture did not conform with that of a sarcoma.

In 1936 Conway<sup>1</sup> collected reports of 56 cases of leiomyoma of the stomach and added 2 cases of his own. These tumors were encapsulated and nodular and bulged on section of the surface. Some were external and projected into the peritoneal cavity; others were internal and invaded the lumen of the stomach and occasionally were accompanied by mucosal ulcerations. The tumors varied in size and were sometimes multiple. The distribution as to sex was practically equal. Some of the tumors caused pyloric obstruction. Conway failed to include the gastric leiomyomas reported by Down,<sup>2</sup> Meyer and Rosi,<sup>3</sup> Martinez and Minnhaar,<sup>4</sup> Villata,<sup>5</sup> Willis,<sup>6</sup> Davidson,<sup>7</sup> Leon,<sup>8</sup> McCarthy,<sup>9</sup> Denham,<sup>10</sup> Kohno,<sup>11</sup> Zakharov,<sup>12</sup> and Millar.<sup>13</sup> The studies of Rieniets<sup>14</sup> would seem to indicate that leiomyoma of the stomach is much more common than has been thought. In the first 100 consecutive post-mortem examinations performed at the Mayo Clinic in 1928, 21 leiomyomas were found in 16 stomachs. A second group of 100 stomachs were found to contain 22 leiomyomas in 16 stomachs. Thirty-four additional leiomyomas in 30 stomachs were found in a third group of unmentioned size. In all, 77 leiomyomas were found in 62 stomachs. In 50 cases there was a single tumor; in 9 cases, 2 tumors; and in 3 cases, 3 tumors. There were 43 males and 19 females. The average age was 59.17 years. Rieniets<sup>14</sup> described a fourth group of 21 leiomyomas removed at operation. In 14 of these cases the tumors were removed primarily because of their size and 7 were removed secondarily in the course of other operations. The average age in these cases was 51.48 years.

In 1932 Melnick<sup>15</sup> reported a case of benign metastasizing leiomyoma of the stomach in which there were metastases in the liver. Davidson<sup>7</sup> describes the x-ray signs of gastric leiomyoma as: "(1) regular filling defect usually between intact curvatures (particularly with submucous growths); (2) signs of external pressure (particularly in pedunculated

subserous growths), (3) abnormally devious but intact rugae (particularly in submucous growths); (4) crater formation (where ulceration has occurred); (5) block in peristalsis (particularly in mural types); (6) filling defects in other organs (notably in duodenum in intragastric pedunculated growths); and (7) obstruction at cardia and pylorus."

Since the publication of Conway's paper, cases of gastric leiomyoma have been reported by Mallory,<sup>16</sup> Lindquist and Mock,<sup>17</sup> Hartman and Camp,<sup>18</sup> Mott,<sup>19</sup> Sworn and Cooper,<sup>20</sup> Toland and Kroger,<sup>21</sup> and Collins and Collins.<sup>22</sup> Pure leiomyomas of the stomach were found 6 times during the period from Jan. 1, 1936, to Nov. 28, 1940, at the Evanston Hospital. They occurred twice in the examination of 7,827 general surgical specimens and 4 times in 653 necropsies, a total incidence of 0.07 per cent.

#### CASE REPORT

M. H., aged 11 years, was admitted to the Evanston Hospital on Oct. 3, 1938, complaining of vomiting of two days' duration and a mass in the stomach. The history was as follows: The child was delivered normally and had had an entirely uneventful period of growth and development up to the present time. On Aug. 25, 1938, she had a bout of "intestinal flu," during which she had postebum vomiting for five days. This cleared up with the use of barley water. There were no other associated abdominal symptoms. At noon on Oct. 2, after having taken canned peach juice, the patient had an attack of nonprojectile involuntary emesis of brown fluid, this was not preceded by nausea. At 7.00 P.M. of the same day she vomited again, several hours after having eaten dinner. At 2 o'clock the following afternoon (the day of admittance to the hospital) she again vomited and the material was found to contain blood.

Inventory by systems showed a loss of 4 pounds in weight during the attack of vomiting in August. This had been regained. There were no symptoms referable to the head or to the cardiorespiratory system. There were no gastrointestinal symptoms other than those referred to, no change of appetite, no food sensitivity, no belching. There were no genitourinary or neuromuscular symptoms. The patient had had measles three years previously. Her tonsils and adenoids had been removed when she was 3 years old.

Physical examination revealed a well developed, moderately well nourished, intelligent, cooperative girl, who was apparently in excellent health. The only significant findings were a slightly injected pharynx and cervical lymph glands that were small, discrete, firm, and bilaterally palpable, being more marked on the left side. The chest and heart were normal. The abdomen showed no marked tenderness or rebound phenomena. In the epigastrium there was palpated an elongate, firm, movable, nodular, slightly tender mass, about  $2\frac{1}{2}$  by  $1\frac{1}{2}$  inches, which seemed to be in the pyloric end of the stomach and which moved with respiration. The abdomen was not distended, but there was some fullness in the right upper quadrant. No peristaltic waves or dilated waves were seen. The abdominal sounds were normal. There were a few palpable inguinal glands. The reflexes were physiologic. No other significant findings were elicited.

X-ray examination revealed a tumor mass encroaching on the duodenal bulb, antrum, and body of the stomach from the lesser curvature. It could not be determined whether the tumor was intrinsic or extrinsic and what its nature was.

Examination of the blood showed 4,390,000 red blood cells, 90.9 per cent hemoglobin, and 9,250 white blood cells. Examination of the emesis fluid revealed a few red blood cells but a plus-3 benzidine test. The feces and urine were normal.

The diagnosis was gastric neoplasm of unknown nature.

Laparotomy was performed on Oct. 4, and a large tumor presented on the outside of the lesser curvature and a tumor mass projected into the cavity of the stomach from the lesser curvature. Gastric resection (Hofmeister-Polya) with anastomosis of the jejunum and proximal portion of the stomach was carried out. The patient was given 250 c.c. of blood during the operation and 250 c.c. postoperatively. No postoperative Wangensteen suction was employed. The patient made an entirely uneventful recovery.

On June 18, 1940, the patient was in fine health and weighed 91½ pounds, a gain of 21½ pounds since November, 1938. There was no evidence of recurrence on physical or x-ray examination at that time. Twenty-five months after the operation was performed the patient was well and was clinically relieved of the disease. The prognosis, however, is guarded.

The pathologic report on the specimen removed was as follows:

*Gross Description.*—The resected portion of the stomach consisted of the pylorus and antrum and a portion of the fundus (Fig. 1). The greater curvature was 13 cm. long; the lesser curvature, 11 cm. long. A nodular tumor mass arose from the lesser curvature and 2 to 3 cm. of the adjacent anterior and posterior walls of the stomach. Toward the pyloric end the tumor grew outward for a distance of 2.5 to 3 cm. to form daughter nodular masses and, at a point approximately 4.5 cm. from the pylorus, it measured 4.5 cm. Numerous engorged blood vessels coursed over the tumor beneath the granular, yellow-pink serosa of the stomach. The red to yellow-gray capsule was 1 to 2 mm. thick. The anterior portion of the large tumor presented a subcapsular cyst 2.5 by 2 cm. Two to three centimeters of the fatty gastrocolic ligament was attached to the specimen. Numerous engorged, tortuous vessels passed from the gastrocolic ligament into the wall of the anterior and posterior surfaces of the stomach.

When the stomach was opened (Fig. 2), a smooth, oblong tumor was seen projecting into the lumen. The distal border abutted against the pylorus. This tumor was 7 cm. long and 3 cm. wide and protruded 1.5 to 2 cm. into the lumen of the stomach. It was covered with a smooth, yellow-pink mucosa. The summit of this tumor presented a recent hemorrhagic erosion of the mucosa, measuring 12 by 10 mm. The muscularis of the pylorus was 6 mm. thick; the mucosa, 2 mm. thick; and the muscularis of the fundus, 3 mm. thick. The mucosa was thrown into folds 10 mm. high. Except for the aforementioned features, the remainder of the normal gray-pink mucosa presented numerous rugae. The intragastric tumor was situated in the magenstrasse and bulged more toward the anterior than toward the posterior surface.

Bisection of the extragastric tumor protruding from the lesser curvature exhibited a fleshy, yellow-white, semifirm, fairly homogeneous structure with an occasional small area of cystic degeneration. Three cysts, measuring from 10 to 20 mm. in diameter, were lined with glistening neoplastic tissue and filled with bloody serous fluid. The small contiguous daughter nodules were composed of homogeneous material similar to that described in the first mass. The intrinsic tumor was contiguous with the extrinsic tumor.

*Microscopic Description.*—Sections from the intragastric portion of the tumor presented one margin covered by an intact gastric mucosa (Fig. 3). The engorged, edematous interstitial tissue of the membrana propria exhibited a slight round-cell infiltration. The normal muscularis mucosae in this section could easily be identified. A narrow layer of edematous submucosa separated the muscularis

Fig 1

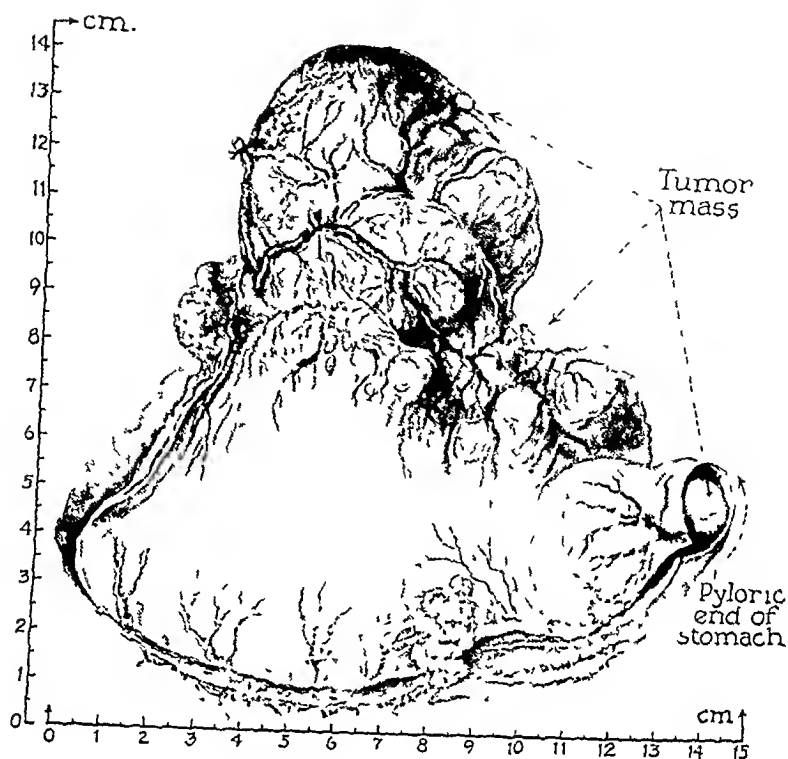


Fig 2.

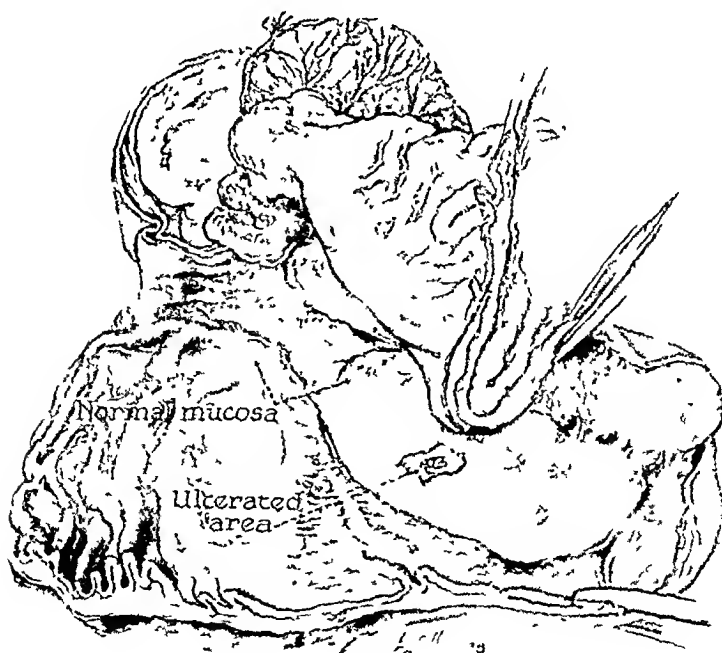


Fig 1—Leiomyoma malignum

Appearance of resected portion of the stomach

Fig 2—Leiomyoma malignum

Appearance of opened stomach



mucosae from the upper margin of the tumor. The tumor contained a moderate number of thin-walled, small, slitlike to oval endothelial-lined spaces. In the main the tumor was composed of anaplastic mesenchymal cells exhibiting considerable hyperchromatism, numerous mitotic figures in the prophase, and slight variation in size and shape (Fig. 4). The numerous anaplastic cells had an irregular, round to oval, smudgy, basophilic nucleoplasm surrounded by a blue-pink, homogeneous



Fig. 3.—Leiomyoma malignum. Section showing covering of intact gastric mucosa.

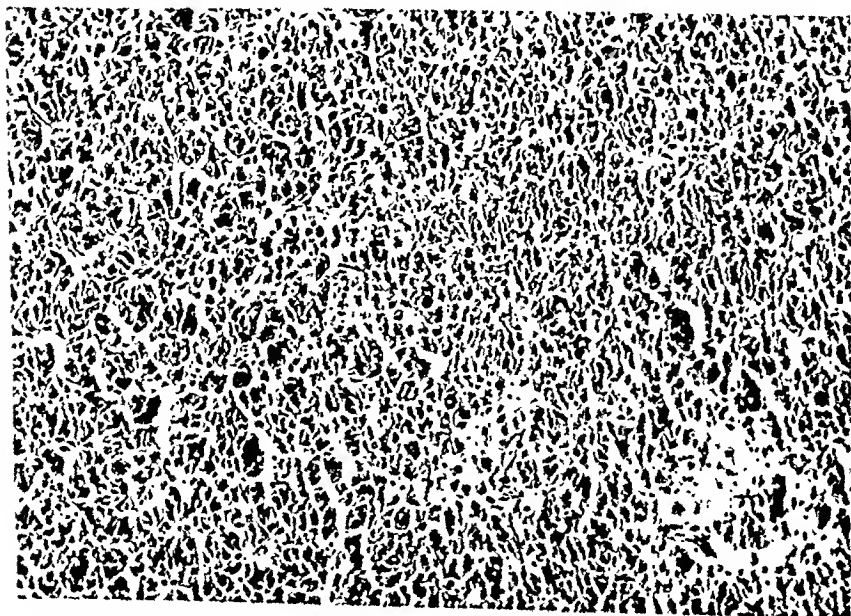


Fig. 4.—Leiomyoma malignum. High power section.

cytoplasm. The more mature cells were elongated and resembled smooth muscle cells. Their blunt, cigar-shaped nuclei presented a uniform distribution of basophilic chromatin with pale blue interstices, a definite nuclear membrane, and an occasional deeper blue-black nucleolus located near one pole. Slender, fibrillar, pink cytoplasmic processes arose from the more mature cells. The latter were growing in bundles or interlacing fasciculi separated by a delicate fibrous connective tissue and small capillaries. Occasionally the more anaplastic cells exhibited multinucleated giant cells.

Masson's trichrome stain identified the tumor cells as composed of smooth muscle. Delicate myoglia fibrils were demonstrated in the more mature muscle cells. Mallory's phosphotungstic-acid hematoxylin stains, although unsatisfactory, revealed blue myoglia fibrils.

Sections from the pyloric wall contained normal mucosa and an edematous, widened submucosa with engorged vessels and hypertrophy of the muscularis. No tumor cell emboli were seen in the veins or lymphatics.

Although no metastases were apparent during the operation on this child, it is thought that the diagnosis of malignant leiomyoma is compatible with the gross and microscopic features present in the tumor.

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# THE EFFECT OF COLLOIDAL ALUMINUM HYDROXIDE ON CERTAIN ASPECTS OF BLOOD COAGULATION

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IN RECENT years colloidal aluminum hydroxide has been advocated clinically in the treatment of bleeding peptic ulcer.<sup>1, 2</sup> At the same time it has been advocated in the laboratory for the total inactivation of prothrombin from blood plasma.<sup>3</sup> As prothrombin-free blood is incoagulable under physiologic conditions, it seemed important to determine whether the anticoagulant properties of aluminum hydroxide had any practical effect on bleeding time in the experimental animal. Furthermore, the closely related substance, aluminum oxide, was found by Dam and Schönheyder<sup>4</sup> to reduce the activity of vitamin K concentrates under certain conditions. Consequently, before giving patients aluminum hydroxide over long periods of time, it seemed worth while to determine whether it might have a destructive effect on vitamin K under controlled dietary conditions. The following experiments were performed to answer these questions.

## EXPERIMENTAL

Two commercial aluminum hydroxide preparations were tested. They were creamalin (Alba Chemical Co.) and amphojel (Wyeth). Both preparations contain finely divided aluminum hydroxide with flavoring material. One part of either of these compounds was found to inactivate the prothrombin in ten parts of human or dog plasma after five minutes' shaking. The prothrombin determinations were done by the method of Quick.<sup>3</sup>

*Experiments on Bleeding Time in Dogs.*—The effect of amphojel and creamalin on the duration of bleeding from skin incisions was measured as follows: Healthy dogs were anesthetized by the administration of sodium amytal intraperitoneally and the abdominal walls were cleanly shaved. Incisions 2 cm. long were then made through the skin in pairs. The two incisions were placed equal distances from the linea alba but on opposite sides. One incision of each pair was used to test the effect of an aluminum hydroxide preparation on bleeding time and the other was treated in the same manner with physiologic saline solution as a control. It was believed that untreated incisions would not provide a fair control because the effect of evaporation might hasten coagulation. It was anticipated that a suspension of particles would tend to hasten

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coagulation, but as a suspension of any material other than aluminum hydroxide would introduce a new variable, it was decided to use physiologic saline solution in the control experiments.

The amphojel, creamalin, and saline solution were applied to the incisions by a slow drip from separatory funnels placed just above the skin level. The rate of drip in the test and control incisions was the same. In each dog care was taken to apply the test substances to some incisions on the right side and to others on the left side. The blood was sponged away from the animal's flanks when it ran down, but the incisions themselves were not sponged. The bleeding time was measured from the time of incision to the time the blood stopped flowing. The fluids that dripped on the wound tended to wash away some red cells from the clot even after bleeding had stopped, but the end point was reasonably distinct.

The 68 control incisions bled for an average of 6 minutes and 32 seconds. The 68 incisions treated with one or the other of the aluminum hydroxide preparations bled an average of 12 minutes and 42 seconds, or an increase of 94 per cent. The 43 incisions treated with amphojel bled for a mean period of 13.7 minutes and the 25 incisions treated with creamalin bled for a mean period of 10.9 minutes.

The effect of these preparations was then tested on incisions made in the mucosa of the small bowel. In some of the animals the loops of the bowel were exteriorized with an intact blood supply after preliminary enteroenterostomy and the exteriorized loop opened after the wound had healed. In other animals acute experiments were done. A loop of jejunum was drawn out and opened along its antimesenteric border, and the mucosal incisions were made at once.

In all of these experiments the parallel pairs of incisions were placed at approximately equal distances from the mesenteric attachment. The incisions were about 1 to 1.5 cm. in length. The mean bleeding time from 14 control incisions was 61.4 seconds. The mean bleeding time from 8 incisions treated with creamalin was 61.6 seconds.

*Experiments on the Effect of Aluminum Hydroxide on the Activity of Vitamin K.*—K avitaminotic white rock cockerels were obtained by growing one-day-old birds in false-bottom cages on Ausbacher's K<sub>1</sub> diet.<sup>5</sup> The water was changed three times a day and fresh diet was supplied twice daily. After eight days blood from the cervical vessels of sample chicks was collected in evaporating dishes. Coagulation time exceeded thirty minutes, the criterion of K avitaminosis accepted by Ausbacher. Thirteen of the chicks were then given vitamin K in the form of cerophyl in the proportion of one part to one hundred parts of diet. Cerophyl is a preparation of dried cereal plants which has been used by us as a source of vitamin K.<sup>6</sup> The amount used was at least four times the amount necessary to protect chicks from K avitaminosis. Another group

of 17 chicks was given the same amount of cerophyl to which had been added creamalin. The resulting diet contained Ansbacher's  $K_1$  diet,\* one hundred parts; cerophyl, one part; and creamalin, ten parts. After four days 3 chicks from each of the three groups were tested for K avitaminosis. Those on the Ansbacher diet alone showed clotting times of over thirty minutes. Those with the 1 per cent cerophyl supplement had clotting times of less than ten minutes, and those of 1 per cent cerophyl plus 10 per cent creamalin also had clotting times of less than ten minutes.

It was evident from these results that creamalin did not interfere with the action of vitamin K in the form of cerophyl in the proportions used, and the proportions were selected with an excess of the aluminum hydroxide preparation and a very moderate dose of vitamin K. As these two ingredients were thoroughly mixed before being added to the Ansbacher diet, there was every opportunity for the action of creamalin.

The remaining birds which had not received vitamin K were treated with 2-methyl-1, 4-naphthoquinone in the proportion of one part per million of diet. Four of the 6 birds received a 50 per cent supplement of creamalin which was mixed with the vitamin K substitute before being added to the diet. The 2-methyl-1, 4-naphthoquinone had a curative effect in all of the chicks regardless of whether or not aluminum hydroxide was present. The findings in this small group of chicks confirmed the experiments in which cerophyl was used.

#### DISCUSSION

The difference in the bleeding time of the skin incisions treated by the aluminum hydroxide preparations seems rather striking, but the variations in individual bleeding times were so great that the results do not have statistical significance; that is, the difference of the means is less than twice the standard error of the differences.

The bleeding time of incisions in the jejunal mucosa appeared not to be influenced by the application of an aluminum hydroxide cream. Neither of the conditions used approximates the bleeding which takes place in certain peptic ulcers in which a sizeable artery is often eroded in a crater which is semirigid as the result of the infiltration of the wall of the ulcer with scar tissue. Unfortunately there appeared to be no way of reproducing severe hemorrhage from a peptic ulcer in the experimental animal.

As aluminum hydroxide is insoluble in water, it would have no opportunity to affect the coagulability of the blood until extravasation had occurred. Presumably clotting to be effective in stopping hemorrhage from an artery would have to occur in the lumen of the vessel. Especially would this appear to be the case with an eroded artery in an ulcer where there would be little, if any, possibility for retraction to occur.

\*A supply of this diet was sent to us by E. R. Squibb & Sons, New York, through the courtesy of Dr. S. Ansbacher and Dr. R. A. Smith.

## CONCLUSIONS

Two commercial preparations of colloidal aluminum hydroxide recommended in the treatment of peptic ulcer were found to be capable of completely inactivating prothrombin in human and dog plasma.

Bleeding time from skin incisions treated with these preparations was longer than in the case of similar skin incisions treated with physiologic saline solution. The difference, however, was not statistically significant.

The bleeding time from incisions in the jejunal mucosa was not influenced by the aluminum hydroxide preparations.

It was found that one of these preparations did not destroy the vitamin K activity of cerophyl nor of 2-methyl-1, 4-naphthoquinone.

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# PERITONEOSCOPY

## AN ANALYSIS OF 150 CASES

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VISUAL examination of the contents of the peritoneal cavity with an endoscope has become a popular diagnostic procedure during the past few years. This revived interest has been occasioned by Ruddock's<sup>1</sup> description of a new peritoneoscopic instrument. Recent reports in the literature have been encouraging without exception. That the peritoneoscope is highly beneficial in a number of conditions has been well established; however, it is feared the impression might be created that peritoneoscopy is advocated for the diagnosis of any and all intra-abdominal lesions. Such a misconception would serve only to bring the procedure into disfavor unjustly. Peritoneoscopy is a satisfactory procedure in selected cases, but, if used indiscriminately, the results will be disappointing.

This paper has for its purpose the critical study of 150 cases of peritoneoscopy in an effort to outline definite indications for the procedure and to call attention to the cases in which this type of examination has been of considerable assistance. On the other hand there is the desire to emphasize the visually inaccessible pathologic conditions in which instances peritoneoscopy would be a useless procedure.

Kelling<sup>2</sup> receives credit as the first to study the peritoneal cavity with a visual instrument. He used a cystoscope for the purpose in 1901, his first subject being a dog. Tedesco,<sup>3</sup> Stolkind,<sup>4</sup> and Roccavilla<sup>5</sup> later utilized various instruments for examination of the peritoneal cavity. In Chicago, Orndoff<sup>6</sup> reported the recognition of intra-abdominal lesions with a visual instrument in 1920. Ruddock,<sup>1</sup> in 1937, described the peritoneoscope and biopsy forceps which are in popular use today. Thieme,<sup>7</sup> in 1939, published fifty cases in detail. In 1939, Benedict,<sup>8</sup> Spangler,<sup>9</sup> Sawyer,<sup>10</sup> and Olim<sup>11</sup> also reported satisfactory results with peritoneoscopy.

### TECHNIQUE

The technical steps in the procedure are quite simple.

Proper interpretation of the findings, however, requires some experience, as would be expected. After a few examinations the observer acquaints himself with the lens system and his findings become more dependable.

No unusual preoperative preparation is necessary for the examination. Morphine is given forty-five minutes previously and combined with scopolamine when disorientation is desired in a nervous patient.

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## CONCLUSIONS

Two commercial preparations of colloidal aluminum hydroxide recommended in the treatment of peptic ulcer were found to be capable of completely inactivating prothrombin in human and dog plasma.

Bleeding time from skin incisions treated with these preparations was longer than in the case of similar skin incisions treated with physiologic saline solution. The difference, however, was not statistically significant.

The bleeding time from incisions in the jejunal mucosa was not influenced by the aluminum hydroxide preparations.

It was found that one of these preparations did not destroy the vitamin K activity of cerophyl nor of 2-methyl-1, 4-naphthoquinone.

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After removal of the obturator the telescope is inserted and the examination begun. The examination should proceed in an orderly fashion whenever possible. A satisfactory routine is to begin in the right upper abdomen with visualization of the right lobe of the liver and gall bladder, proceeding then to encircle the peritoneal cavity clockwise returning to the original starting point. Following this preliminary inspection attention may be concentrated upon the area of suspected pathology.

When masses are present, palpation can be combined with visualization by simply releasing air from the peritoneal cavity until the mass becomes palpable. It is possible to determine mobility of a mass with this method and, by observing the degree of indentation of the examining fingers, to learn whether the mass in question is solid or cystic. Change in position of the patient enables the examiner to increase his scope of visibility. Trendelenburg's position combined with pelvic manipulation by an assistant will usually serve to bring prolapsed pelvic organs into view. Fowler's position permits the liver to drop downward and aids in inspection of the upper surface of the liver and the diaphragm. With the patient lying on his right side the air will gravitate to the left upper abdomen and the small spleen will drop into view. The enlarged spleen can be seen easily when the patient is in a supine position.

The Ruddock biopsy forceps is an ingenious addendum. A small telescope in the forceps permits the taking of biopsies under direct vision and the tip of the instrument serves as the coagulating medium. It is possible to secure the biopsy and thoroughly coagulate the denuded area immediately, as insulation in the coagulating tip prevents charring of the specimen.

At the completion of the examination the telescope is withdrawn and the air is evacuated. Following this the sheath is removed and the skin edges approximated with one or two clips. No attempt need be made to close the deeper tissues except in infants, when one suture is advisable due to the thinness of the abdominal wall. Postoperatively the patient should be kept in bed for twenty-four hours after which time he may resume his activities.

#### SELECTION OF CASES

The proper selection of cases is an important phase of peritoneoscopy. Only those organs lying superficially within the peritoneal cavity are suitable for visualization. Roughly speaking, peritoneoscopy will permit the observer to see just as much of the abdominal contents as would be possible with the naked eye if the entire anterior abdominal wall were absent, plus those organs brought into view through changes in position of the body. Fig. 2 classifies diseases according to their ease of diagnosis by peritoneoscopy.

*Cirrhosis of the Liver.*—The liver lends itself well to peritoneoscopy. After a reasonable amount of experience any deviation from normal in the liver may be readily recognized.

Breakfast is withheld to prevent a distended stomach from interfering with vision and care is taken to have the bladder empty before sending the patient to the operating room.

Local infiltration with novocain is used in all cases except infants and children when general anesthesia must be employed. A small stab incision is made just below the umbilicus in the average case, although the site of the incision may be varied, depending upon the presence of subumbilical scars or large masses. A nick in the anterior rectus fascia

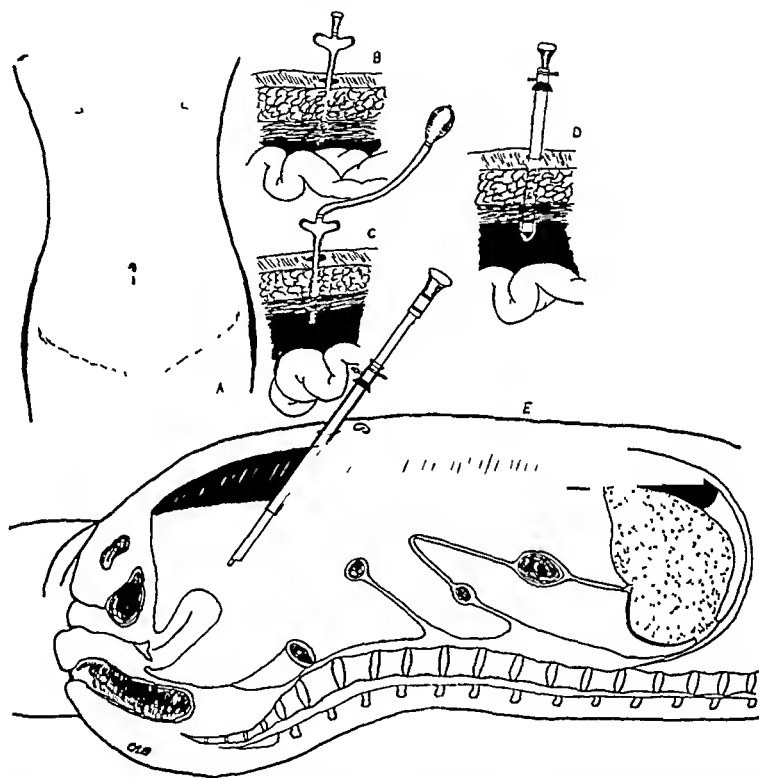


Fig 1.—Technique of peritoneoscopy. A, Usual location of stab incision; B, introduction of pneumoperitoneum needle; C, pneumoperitoneum produced with atmospheric air; D, trocar introduced; E, telescope in position for viewing pelvic organs.

facilitates passage of the pneumoperitoneum needle, the peritoneum itself offering practically no resistance. Pneumoperitoneum is created with atmospheric air introduced by an ordinary hand bulb. At this point the needle may be moved about gently to determine the presence of adhesions as a guide for later passage of the trocar. No attempt is made to measure the amount of air introduced, as the quantity varies greatly depending upon the size of the abdomen, the presence of ascites, or large masses. When a moderate pneumoperitoneum exists, the trocar is inserted at an angle to either side of the vertebral column in order to prevent injury of an intestinal loop against that bony structure.

tween cirrhosis of the liver and malignancy is difficult. The prognosis in the two cases may differ considerably. Neither is surgical. Peritoneoscopy offers a satisfactory solution of the diagnosis.

*Jaundice.*—Jaundice alone is not sufficient indication for peritoneoscopy. Acute catarrhal jaundice in the young adult reveals nothing unusual other than a smooth, jaundiced liver and bile-stained organs. In a case of obstructive jaundice the peritoneoscope may show a distended thin-walled gall bladder as presumptive evidence of carcinoma of the head of the pancreas or a thick-walled contracted gall bladder which will shift the evidence toward a diagnosis of common duct stone. In either condition, however, the peritoneoscope does not reveal the complete picture, as it is impossible in most cases to visualize the pancreas or the common duct. This type of case should be considered surgical in order that the patient can receive the benefit of exploratory laparotomy. Jaundice cases warrant a peritoneoscopic examination only when additional symptoms indicate possible malignancy of the liver, gall bladder, or a cirrhosis of the liver.

*Tuberculous Peritonitis.*—The peritoneoscope has one of its greatest fields of usefulness in this condition. The diagnosis may be readily made in most cases and in the occasional case of peritoneal carcinomatosis, when the differentiation is confusing, a biopsy will clarify the diagnosis.

The pneumoperitoneum was purposely undisturbed in all cases on completion of the examinations. Two of the thirteen cases appeared to receive some benefit from the retained air as shown by diminished temperatures, although the remaining eleven cases revealed no changes.

*Peritoneal Malignancy.*—There were eight cases of peritoneal carcinomatosis in this series, all revealing typical findings. The peritoneoscope offers a high degree of accuracy in these cases. If any question exists, a biopsy may be taken without hesitation because of the relative avascularity of the peritoneum.

*Ectopic Pregnancy.*—Two cases of ectopic pregnancy were observed, both being ruptured tubal pregnancies. Of all the peritoneoscopic examinations performed, none were more satisfactory from a diagnostic standpoint than these two cases. Free blood was conspicuous in the peritoneal cavity and visualization of the pelvis in Trendelenburg's position showed the point of tubal rupture in each instance. Most cases of ectopic pregnancy are obvious. Peritoneoscopy, however, will be of service in cases of rupture when the diagnosis is questionable. Nonruptured ectopic pregnancies may sometimes be indistinguishable from uterine pregnancies. The Aschheim-Zondek test would be of no value in these cases. Peritoneoscopy should solve the problem without disturbing an existing uterine pregnancy.

*Intraperitoneal Hemorrhage.*—Suspicious hemorrhage can be detected promptly with the peritoneoscope. One case of possible spontaneous hemorrhage was examined and the peritoneal cavity was found to be

Cirrhosis of the liver presents an unmistakable picture. The hobnail variety can be recognized at a glance, while early cirrhotic changes may be safely predicted by the experienced observer. It has been enlightening to discover a high percentage of cirrhotic livers in patients with deep jaundice, since jaundice is ordinarily not emphasized in medical textbooks as a prominent symptom of the disease. Peritoneoscopy is indicated in all questionable cases of cirrhosis, chiefly as an aid to prognosis.

### CLASSIFICATION OF CASES EXAMINED

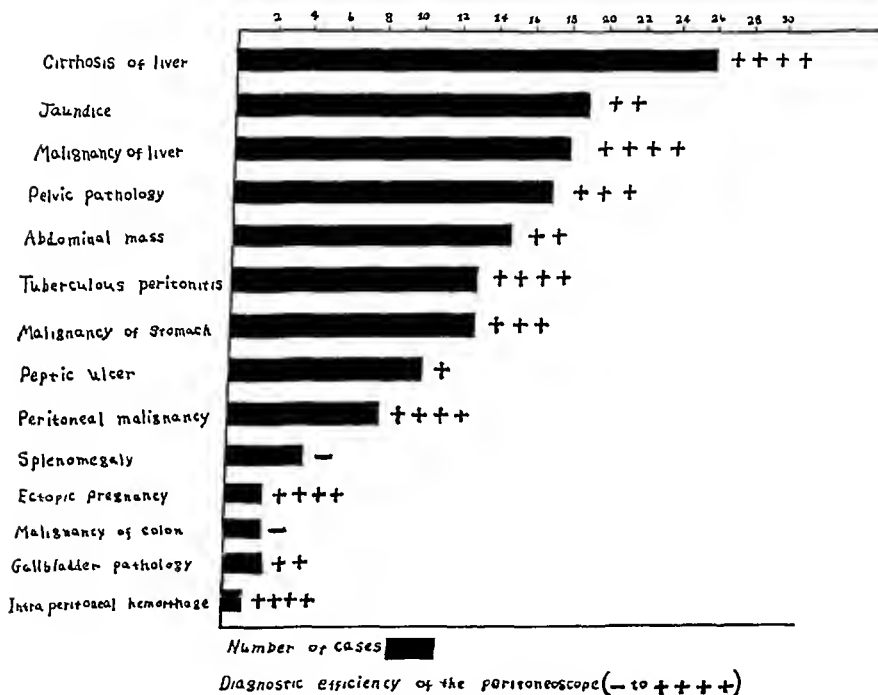


Fig. 2.—The cases examined comprise fourteen different pathologic conditions. Cirrhosis of the liver was the most common pathology seen with a total of twenty-six cases. Splenomegaly and malignancy of the colon are not considered indications for peritoneoscopy. The other types of pathology are classified from a 1 plus to a 4 plus, depending upon the ability to diagnose peritoneoscopically.

It will be noted in Fig. 2 that there were twenty-six cases of cirrhosis examined, the largest group of cases in the series. Because of the gratifying results, a four-plus efficiency has been awarded the peritoneoscope for this condition.

*Malignancy of the Liver.*—Suspicious malignancy of the liver is likewise a prime indication for peritoneoscopy. The picture is typical and easily recognized. The diagnosis is usually so definite that it is unnecessary to resort to biopsy. By shifting the patient's body it is possible to examine carefully the surfaces of the liver so that the smallest superficial nodule may be seen. Frequently the clinical differentiation be-

have a resectable lesion. The four remaining patients recommended for laparotomy because of absent visible metastases all had lesions involving the pancreas and were nonresectable.

Peritoneoscopy will prevent unnecessary surgery in a fair proportion of cases of carcinoma of the stomach. Those patients without visible metastases and obvious local involvement will not be jeopardized, as laparotomy can be done to determine operability definitely.

*Peptic Ulcer.*—The peritoneoscope was used in eleven cases of suspected peptic ulcer, two of which were possible perforations. Practically all of these examinations were carried out during the earlier experience with the instrument.

## OPERABILITY OF CARCINOMA OF STOMACH

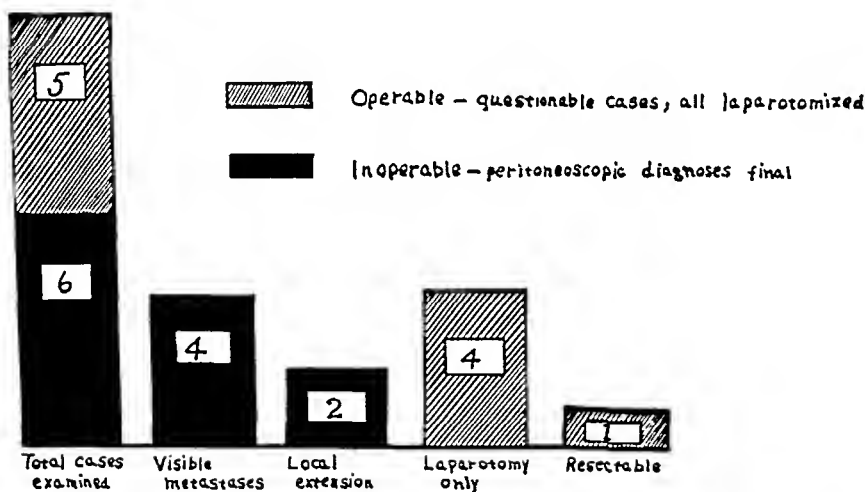


Fig. 3.—Eleven cases of carcinoma of the stomach were studied. Six were considered inoperable, while only five were recommended for laparotomy after peritoneoscopic examination.

Insignificant serosal changes accompanying an ulcer of the stomach may be overlooked with the peritoneoscope. The duodenum cannot be visualized in a sufficient number of cases to make the procedure trustworthy. Both roentgenographic examination and the gastroscope have far more diagnostic value in these cases. The use of the peritoneoscope may be reserved for the small group of cases in which an ulcer perforation is so atypical that there is hesitation of laparotomy, yet the fear exists of allowing the optimal time of operation to pass.

*Pelvic Pathology.*—Visualization of the pelvic organs can usually be carried out with a high degree of success, particularly when combined with manipulation per vagina. Questionable ectopic pregnancy has been discussed previously as an important indication. Ovarian or uterine tumors lend themselves well to inspection. Biopsies of such tumors are of material assistance and may be taken readily in the average case.

filled with blood. Operation later revealed a varix of the omentum which had ruptured. Coleman<sup>12</sup> reports the use of a small trocar to determine the presence of intraperitoneal hemorrhage. A slightly larger trocar may be used, however, to accommodate the peritoneoscope with the added advantage of visualization in those cases where no greatly increased intra-abdominal pressure exists to force the blood out through a trocar.

There is a place for peritoneoscopy in cases of possible intra-abdominal hemorrhage without external evidence of injury. Such patients, frequently the victims of automobile accidents, have head injuries which serve to confuse the picture. The peritoneoscope may prevent unnecessary laparotomies in this type of critically ill patients.

*Malignancy of the Stomach.*—There were twelve cases of malignancy of the stomach. One case was diagnosed peritoneoscopically as sarcoma with a confirmatory biopsy. An additional case in which no tumor could be seen with the peritoneoscope proved to be a gastric ulcer at operation. Only those lesions involving the anterior wall of the stomach can be seen. In the obese type of individual the stomach is often completely obscured by the liver; nevertheless, a little practice enables the examiner to elevate the liver with the tip of the instrument and to study the stomach at close range. Distention of the stomach by an indwelling nasal catheter will usually roll that organ out into view.

It is the status of the malignancy on the posterior wall, however, that cannot be determined with the peritoneoscope. It is impossible to learn whether the lesion has penetrated into the pancreas or not. Because of this deficiency only a three-plus accuracy is awarded the peritoneoscope in diagnosis of malignancy of the stomach. (Fig. 2.) In spite of the admitted inadequacy of the peritoneoscope, the results in this series of cases suggest that all carcinomas of the stomach be routinely peritoneoscoped. This measure is not aimed at diagnosis of the lesion in the stomach per se, as roentgenographic study is more capable of such, but rather at the determination of operability of the case.

It is generally agreed that metastases to the liver and peritoneum render a patient inoperable with the exception of palliative surgery in the obstructive type of lesion when a gastroenterostomy will give temporary relief. In this series of eleven cases of carcinoma of the stomach, four had liver metastases, while two others were considered inoperable because of marked local extension into the peritoneum and adjacent organs. Of these latter two cases one died three weeks later of cachexia. Hence six, or 54 per cent, of these cases were grossly inoperable and were saved from needless surgery by the peritoneoscopic examination (Fig. 3.) Of the five cases recommended for surgery, one was considered clinically inoperable because of palpable abdominal masses thought to be peritoneal metastases. On peritoneoscopy these masses were discovered to be epigastric hernias. At operation this patient was found to

Peritoneoscopy should be used for abdominal masses when clinical diagnostic measures have failed, bearing in mind that the instrument will offer little or no assistance unless the mass is superficially placed.

*Gall Bladder Pathology*—Because of its exposed position the gall bladder offers no obstacles to visualization. The normal robin's egg-blue color is distinct and any variations are easily noted. Acute cholecystitis gives an unmistakable picture. Malignancy of the fundus may be recognized without difficulty.

In many instances, however, examination of the gall bladder is not complete or dependable unless the extrahepatic bile ducts can be examined also for pathology. The peritoneoscope cannot visualize the biliary duct system and hence this examination is not recommended for cases in which such pathology is likely. If interest centers on the gall bladder alone, peritoneoscopy will be entirely satisfactory.



Fig. 5—Carcinoma of the stomach with serosal involvement viewed through the peritoneoscope.

No gallstones have been palpated with the tip of the instrument as described by Steiner;<sup>13</sup> nevertheless, it should be easy to palpate a large barrel-shaped stone in a contracted gall bladder that was partially empty of bile. Small stones floating in bile obviously would be difficult to palpate.

*Splenomegaly*.—The enlarged spleen is easily seen with the peritoneoscope. The small spleen is brought into view by placing the patient on his right side.

Pelvic inflammatory disease, however, may offer difficulties to the examiner and it is because of this condition that a three-plus efficiency is allotted in Fig. 2. Both recent and old pelvic inflammatory processes frequently result in adhesions between the pelvic organs with obliteration of landmarks so that it may be impossible to classify distinctly the status of the organs. A tubo-ovarian abscess may be fused with the uterus so that normal boundaries are indistinct. The surgeon will appreciate this situation, as the same difficulty often exists at laparotomy and blunt dissection must be carried out before the adherent organs are mobilized sufficiently for identification to be made.

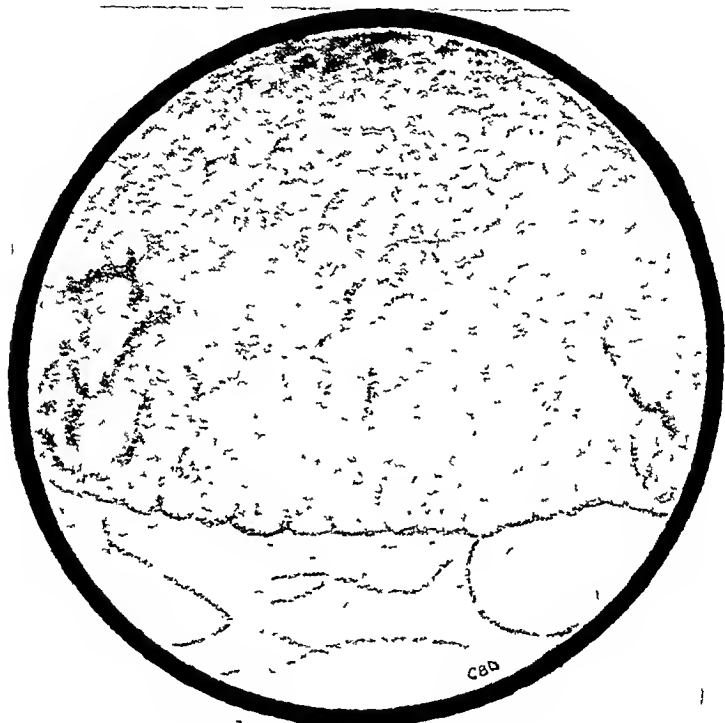


Fig 1—Advanced hobnail cirrhosis of the liver as seen through the peritoneoscope

*Abdominal Masses.*—If the abdominal mass lies superficially in the peritoneal cavity, its diagnosis may be simple and spectacular. If covered by omentum, intestines, or other organs, it may be impossible to arrive at a definite diagnosis. Hydrops of the gall bladder, cysts or tumors of the liver, tumors of the stomach, and masses arising from the pelvis are easily differentiated. A large cyst almost filling the peritoneal cavity will be noted as such, but the likelihood of determining its origin will be slight unless the cyst can be moved about with change in position of the body. Retroperitoneal tumors can only be diagnosed as such, although in one instance the diagnosis of tumor of the right adrenal gland was made while totally unsuspected clinically, and operation verified the peritoneoscopic findings.



of intestinal perforation due to adhesions between the visceral and parietal peritoneum.

#### ACCURACY OF PERITONEOSCOPY

A follow-up of patients reveals that the diagnoses have been proved in 44 of the total 150 cases. The final diagnoses have been made by either autopsy, operation, or biopsy. These 44 cases have been utilized as a check against the accuracy of both clinical and peritoneoscopic diagnosis. Fig. 7 contains these statistics.

Of the 44 diagnoses substantiated, the clinical diagnosis was correct in 24 cases, giving a clinical accuracy of 54.5 per cent. The peritoneoscopic diagnosis was found to be correct in 40 of the cases, with an accuracy of 90.9 per cent. These statistics compare rather closely with those compiled by Ruddock.<sup>1</sup> The peritoneoscopic accuracy should remain consistently high if there is a proper selection of the cases to be examined.

#### ACCURACY OF THE PERITONEOSCOPE

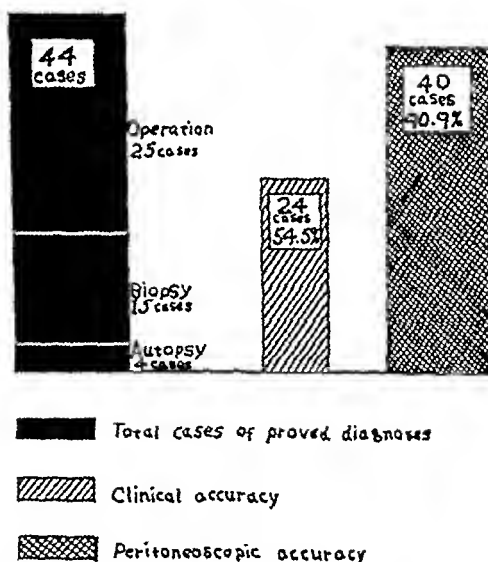


Fig. 7.—There were forty-four cases with diagnoses proved by either operation, biopsy, or autopsy. The accuracy of both clinical and peritoneoscopic diagnoses is shown.

The four peritoneoscopic errors consist of: (1) diagnosis of ovarian cyst proved at operation to be a tubo-ovarian abscess; (2) failure to recognize an acute yellow atrophy of the liver in a young male, diagnosis clarified by autopsy; the peculiar splotching of the liver was described at peritoneoscopy, but its true significance was not appreciated; (3) peritoneoscopic diagnosis of abdominal Hodgkin's disease which at autopsy proved to be a metastatic carcinoma; (4) inability to determine the nature of a deeply situated abdominal mass; operation revealed the mass to be carcinoma of the mesentery.

In Fig. 2 it will be noted that splenomegaly is not considered now as an indication for peritoneoscopy. Splenomegaly itself is diagnosed by abdominal palpation. Visualization of the spleen, although easily accomplished, is usually disappointing because of the difficulty in interpreting gross appearances. No aid is to be had from the microscope, as biopsy of that organ is too hazardous for safety. Blood studies and the clinical history will usually give decidedly more information about a splenomegaly than the peritoneoscope can offer.



Fig. 6.—Ruptured right tubal pregnancy, peritoneoscopic view. Note the large clot adherent at the site of rupture.

*Malignancy of the Colon.*—The peritoneoscope should be used only for the determination of operability of malignancy of the colon in cases where liver metastases are suspected. Neither the colon nor small intestine is accessible in a sufficient number of cases to make the procedure dependable. The loop of intestine containing the pathology might be obscured by other loops with the result that the diagnosis will be missed.

*Appendicitis and Peritonitis.*—In view of the fact that the appendix is retrocecal in the majority of cases it is no wonder that it is rarely seen. These observations on the accessibility of the appendix have been made in cases with other than appendiceal pathology in which the appendix has been searched for as a routine measure. Peritoneoscopy is definitely contraindicated in suspected cases of acute appendicitis.

Acute peritonitis from any cause should be avoided. The possibility of activating such an infection is great and there is the increased danger

Evidence points toward the safety of close observation without immediate laparotomy in those cases where adhesions are suspected due to the superficial position of the involved intestine. If there exists considerable doubt in the examiner's mind of sufficient mechanical protection for the site of perforation, then immediate laparotomy should be performed.

The one fatal accident was caused by an error on the part of the examiner. The patient with a known mediastinal tumor was found to have multiple abdominal masses on peritoneoscopy. An attempt was made to secure a biopsy of an apparent liver nodule with the result that a cholangitic abscess wall was perforated. Care in palpation of the mass in the liver with the tip of the instrument would have shown its true cystic nature and prevented the accident. Bile was seen to escape from the perforation, but, in view of the patient's widespread malignancy and poor condition, operation was decided against.

There have been but few additional complications with the peritoneoscope. Occasional cases of mild subcutaneous emphysema have been noted, but all subsided rather promptly. There were no hernias, wound infections, or hematomas in the series. There was only one instance of shoulder pain from pneumoperitoneum, which occurred in a patient with a ruptured tubal pregnancy. She complained of right shoulder pain shortly after inflation of the peritoneal cavity was begun. It is interesting to observe that the peritoneal cavity may be inflated to its maximum without the production of shoulder pain, while many cases of such pain are reported following the injection of much smaller quantities of air during tubal patency tests. Even extreme Fowler's position in greatly inflated cases has not been productive of shoulder discomfort. No explanation is offered for the apparent paradox.

#### SUMMARY AND CONCLUSIONS

1. The present report is based on 150 personal cases of peritoneoscopy. Statistics are presented in an effort to aid in the selection of cases suitable for this type of examination.

2. The technique of examination is described. The procedure is essentially the creation of a pneumoperitoneum followed by the introduction of a telescope which permits the observer to view the peritoneal cavity and its superficial organs in detail with a clear undistorted vision.

3. Biopsies of organs in the peritoneal cavity may be taken with safety by the use of a special telescopic forceps developed by Ruddock.

4. Emphasis has been placed on the selection of cases. Only those organs which either lie superficially in the peritoneal cavity or may be brought into a superficial location by change in position of the body or by manipulation are amenable to visualization. Failure to consider these facts will usually be productive of disappointing results.

A glance at these so-called peritoneoscopic errors will reveal that the first three are actually personal errors, failures to recognize visible pathology, while only the last one is a true mechanical error, attributed to an inability to bring the pathology into view.

#### ACCIDENTS AND COMPLICATIONS

There were three accidents in this series of cases (Table I). The two nonfatal accidents were intestinal perforations, in one with the pneumoperitoneum needle, in the other with the trocar. No operation was done in either case.

TABLE I  
ACCIDENTS AND COMPLICATIONS

PERITONEOSCOPIC DIAGNOSIS	ACCIDENT	RECOVERED	DIED
None (Clinical, peritoneal carcinomatosis)	Pneumoperitoneum needle introduced into intestine; paracentesis 2 days previously	No operation; no evidence of peritonitis	
None (Clinical, tuberculous peritonitis)	Trocar entered intestine	No operation; recovered without peritonitis or wound infection	
(Abdominal, Hodgkin's disease)	Perforation of small cholangitic abscess with biopsy forceps while attempting biopsy of liver nodule; accident recognized but, in view of widespread metastases and poor condition, operation thought unwise		Died 7 days later; autopsy: bile peritonitis, carcinoma of head of pancreas with metastases to peritoneal cavity and mediastinum
RESULTS			
		CASES	MORTALITY RATE
Total cases examined		150	
Accidents		3	
Deaths		1	0.6%

Because of the ease with which the instruments perforated the intestines just as the peritoneum was entered, it was concluded that the involved loops were firmly adherent at the points of perforation and that the general peritoneal cavity would not be soiled. Both patients were observed very carefully for signs of beginning peritonitis, but none appeared. Their recoveries were uneventful without even a wound infection in either case.

Many observers have noted that nonadherent intestinal loops will slip away from the trocar. Kelling<sup>14</sup> called attention to this phenomenon. Ruddock<sup>1</sup> reported bowel perforation in eight of his cases, all of them being operated upon shortly afterward. He found that, in view of dense adhesions between the perforated intestines and the parietal peritoneum, no peritoneal soiling would have occurred in any of the cases.

The decision as to whether or not to explore following the perforation of an intestine should depend upon circumstances surrounding the case.

# SELF-INTRODUCED FOREIGN BODY PERFORATING LARGE BOWEL

## OPERATION WITH RECOVERY

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FOREIGN bodies in the large bowel have been reported by Branning, Pamperi, Neese, Koucky and Beck, and many others. These cases are always interesting and instructive. The case I am reporting presents a few unusual features which will be discussed.



Fig. 1.—Roentgen ray disclosing screwdriver in region of splenic flexure.

CASE REPORT.—N. J. (No. 19956), a 35-year-old colored male, entered the Cook County Hospital on April 8, 1940, stating that during the preceding week he had developed a tender swelling in the left inguinal region which extended into the scrotum. He had had a small "lump" on the left side since he was 2 years old and he had always been able to push the "lump" back until recently, when it had become "big and sore." He further stated that he also had a "falling of the intestines" (prolapsed rectum). His rectal prolapse became excessive seven days prior to his admission to the hospital while he was carrying wood. To replace his prolapsed rectum, he went to his shack and procured an 8-inch screwdriver which he placed, handle first, into his anal orifice. The prolapse was relieved. Much to his surprise, he lost control of the screwdriver and it too disappeared. He attempted to extract it, first with his fingers and then with a soup spoon. These attempts having failed, he desisted from further effort. It was at this time (seven days

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5. The conditions affording the most satisfactory results with peritoneoscopy may be listed as follows: cirrhosis of the liver, malignancy of the liver, tuberculous peritonitis, peritoneal malignancy, ectopic pregnancy, intraperitoneal hemorrhage, pelvic pathology, and the determination of operability of malignancy of the stomach.

6. An analysis is made of 44 cases in which the diagnosis was proved by either operation, biopsy, or autopsy. In this group the clinical diagnosis was accurate in 54.5 per cent of the cases while a 90.9 per cent accuracy was obtained with the peritoneoscope.

7. There were 3 accidents in the series of 150 cases, only 1 of which was fatal, giving a mortality of 0.6 per cent. It should be considered that a large number of the patients examined were bad risk cases that were subjected to peritoneoscopy with the hope that laparotomy could be avoided if possible.

8. In comparison with laparotomy, peritoneoscopy is a minor operative procedure with very little discomfort to the patient and economically important in that it requires only one day of hospitalization, following which the patient may become ambulatory.

9. Peritoneoscopy has proved to be a valuable adjunct in diagnosis. It is not a fad but rather a procedure which has definite indications and limitations. The peritoneoscope will not supplant laparotomy but will render operation unnecessary in many cases. On the other hand, following peritoneoscopy a number of cases will be revealed as surgical that were not considered so beforehand.

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into the scrotum. It was very tender, irreducible, and did not transilluminate. Rectal examination revealed no prolapse or hemorrhoids, hence this phase of his story was doubted. No masses or foreign bodies could be felt.

The patient was subjected to fluoroscopy and x-ray examination revealed a screw-driver, the handle of which lay in the region of the splenic flexure (Fig. 1). The jagged end of the tool lay near the junction of the descending colon and sigmoid.

The patient was given a morphine-scopolamine sedative followed by a local infiltration with novocain in the inguinal region. He developed a scopolamine "jag" and became so uncooperative that nitrous oxide anesthesia was resorted to. A left inguinal incision was made and the aponeurosis of the external oblique muscle was divided. The hernial sac and spermatic cord were delivered. On opening the sac, free serous fluid gushed out. The omentum was firmly attached to the lateral wall of the sac which necessitated its being cut between two hemostats and then ligated. The omentum, freed from its distal attachment, was inspected and found to be very hard and fibrotic. This indurated area, measuring 29 by 2½ cm., was resected. The omental stump was replaced into the peritoneal cavity (Fig. 2).

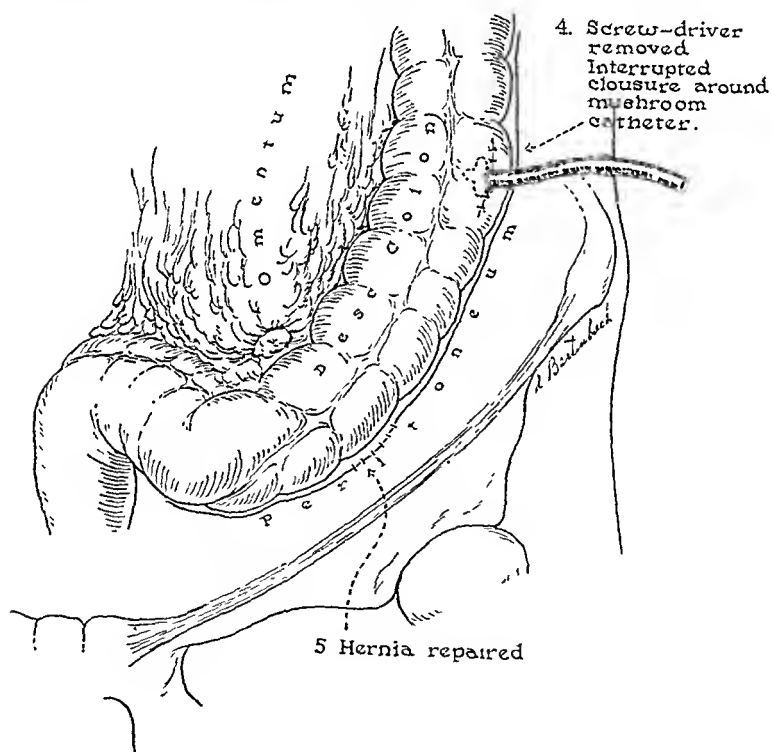


Fig. 3.—Final steps of operation.

Traction was made on the hernial sac and the sigmoid was found to be attached to the lateral sac wall. The diagnosis of a sliding hernia was made. The tip of the screwdriver could now be felt. Two perforations were found in the sigmoid in the region occupied by the jagged tip of the screwdriver. An opening was made in the bowel, beginning at the sigmoid perforations and extending about 2 inches cephalad into the descending colon. This incision connected both perforations, converting these into one opening. Through this opening the screwdriver was delivered. A de Pezzer catheter was placed into the defect which was closed by

before his entrance) that his inguinal hernia became irreducible. He managed to hitchhike his way to Chicago, a distance of about 400 miles. During this four-day trip he noticed that he still could not reposit the inguinal hernia, although he experienced no discomfort. A day after his arrival in Chicago his scrotal mass and inguinal region became painful and tender. The pain was not severe but was aggravated by walking and coughing. During the ensuing two days the mass became more painful and he thought he should have a doctor see it. He did not vomit and he had his last bowel movement two days before entering the hospital.

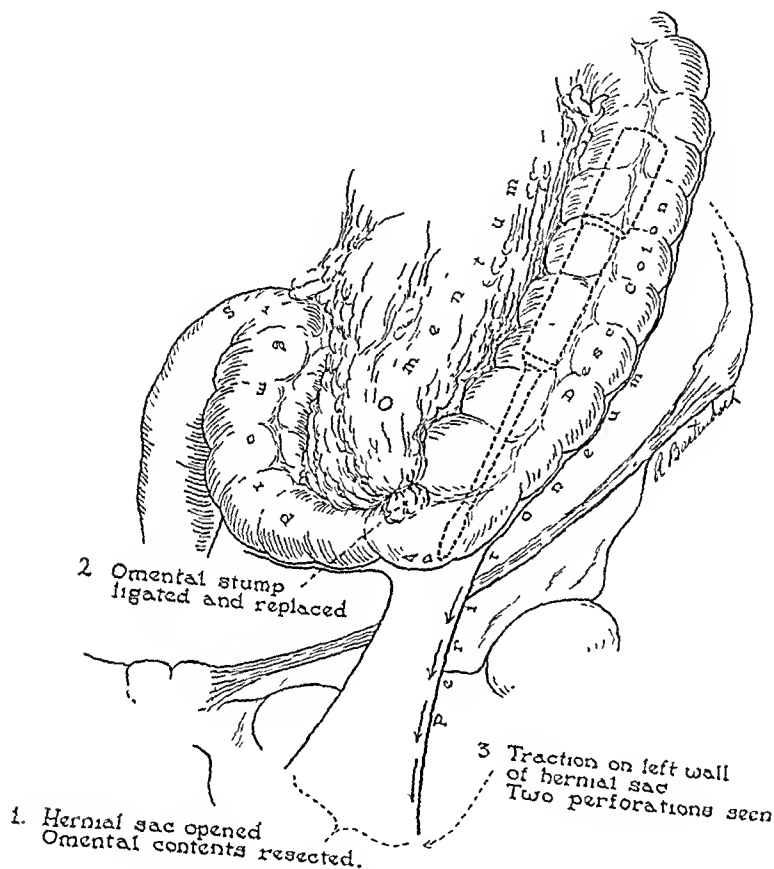


Fig. 2.—Steps of operation diagrammatically outlined.

His past history revealed that he had had a right herniorrhaphy five years before, gonorrhea several times, and had been treated for syphilis in 1926. Physical examination revealed a well-developed and well-nourished colored male who did not appear acutely ill. His temperature was 100.2° F.; his pulse, 80; and respirations, 20 per minute. His blood pressure was 100/82. The abdomen was flat (tumbilous on the xiphopubic line). Tenderness was present over the left upper and lower quadrants. The patient stated that he could feel the screwdriver in his left upper quadrant, but this could not be verified by the examining physicians. No masses were palpable. Peristaltic sounds were present but diminished (six to eight per minute). The sounds were not those of obstructive bowel obstruction but resembled normal clicks and gurgles. The left inguinal region presented a mass which extended



# EXCISION AND/OR PROXIMAL LIGATION OF EXTRAOSSEOUS THROMBOPHLEBITIS IN THE TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS WITH POSITIVE BLOOD CULTURE

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THE following case is reported (1) because it demonstrated particularly well the thrombophlebitic nature of the local bone lesion of acute hematogenous osteomyelitis; (2) because it demonstrated the relationship of the bacteriemia to the local bone lesion; (3) because it showed marked similarity to cases of mastoid disease with jugular vein thrombosis; (4) because the thrombophlebitis made an important indication for treatment; and (5) because it demonstrated the necessity for looking for similar accessible thrombophlebitis in all other cases of acute hematogenous osteomyelitis with bacteriemia with the idea of excision or proximal ligation of such affected veins draining the bone focus in order to control the general infection.

## CASE REPORT

(Doctor's Hospital, No. 25649, Feb. 22 to March 9, 1940) In a boy 12 years of age with a negative family history and a previous history of a pneumococcus meningitis at the age of 2 years with recovery except for a residual bilateral complete deafness a small infection of the right big toe (paronychia) was followed by a focus of osteomyelitis in the upper end of the left tibia. At the time of admission to the hospital, the patient was markedly toxic, had a high temperature, and was stuporous.

The bacteriologic studies showed a *Staphylococcus aureus* bacteriemia of the magnitude of 12 colonies per cubic centimeter of blood cultured. The patient was put on an adequate dosage of sulfanilamide and, later, sulfathiazole. However, there was no effect of the chemotherapy upon the bacteriemia, although the general condition of the patient improved somewhat, and the local condition continued unchanged. Several days after admission a thrombophlebitis of the saphenous vein was noted and the latter could be traced as extending directly from the area of the osteomyelitis in the head of the tibia upward and downward into the adjoining segment of the saphenous vein. The indication for excision of the vein seemed obvious and the similarity to cases of acute mastoiditis with jugular vein thrombosis was noted.

This was confirmed at the operation. There was a suppurative inflammation of the skin and subcutaneous tissue over the inner condyle of the tibia; the thrombophlebitis of the saphenous vein originated in this area which was continuous with the focus of osteomyelitis; and it was possible to dissect out and remove the entire thrombosed vein well into healthy tissue both above and below. The bone itself was not touched in any way. The wound was left wide open and packed with iodoform gauze.

The bacteriemia disappeared immediately thereafter. The local wound from which the vein had been removed healed very well and at the end of two weeks the boy was discharged from the hospital.

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interrupted through-and-through catgut sutures around the catheter. One of these sutures was passed through the catheter to anchor it to the bowel wall. No second layer of sutures was placed because of fear of tension. A stab wound was made in the left loin and the catheter pulled through this. The hernial sac was then ligated distal to the sigmoid attachment. A modified Bassini repair with interrupted catgut sutures completed the operation. (Fig. 3.) One cigarette drain was placed subcutaneously.

For two days following the operation the patient's rectal temperature mounted to 103.8° F. The pulse also reached its maximum of 120 during these two days. Following this the temperature and pulse steadily dropped until the eighth post-operative day when normal levels were reached and maintained. His convalescence was quite uneventful. The mushroom catheter was removed on the seventh post-operative day. The colostomy site stopped draining on the twentieth day. He received by transfusion 1,000 c.c. of citrated blood and 100 c.c. of 0.8 per cent sulfanilamide solution subcutaneously. He was kept on intravenous dextrose and saline solution for the first three postoperative days. He was discharged in good condition twenty-two days following the operation.

#### SUMMARY AND COMMENT

1. A case of a large, sharp, foreign body, self-introduced and perforating the bowel with soiling of the peritoneum, is reported.

2. The foreign body was removed surgically and recovery resulted.

3. While throughout the entire procedure the operative field, intra- and extraperitoneal, was grossly contaminated with feces and while the only drainage used was a rubber tube in the large bowel and one subcutaneous cigarette drain and no attempt was made to cleanse the peritoneal cavity, infection remained localized. Whether or not the two small bowel perforations created some sort of intraperitoneal vaccination remains *sub judice*.

4. Abdominal auscultation aided in suspicion of intraperitoneal damage because the intestinal sounds were definitely diminished.

5. Retroperistalsis obviously played a part in determining the final position of the foreign body since the handle abutted the splenic flexure.

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# MESODERMAL MIXED TUMORS OF THE CORPUS UTERI

## REPORT OF A CASE WITH REVIEW OF THE LITERATURE

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### INTRODUCTION

IT IS our purpose to describe an instance of an extremely rare tumor, the mesodermal mixed tumor of the body of the uterus. It belongs to a remarkable group of bizarre tumors which originate from cells normally absent in the uterus. After a painstaking review of the literature of mixed tumors, sarcomas of the simple and more complicated types, teratomas, lipoma, chondroma, osteoma, etc., of the cervix and corpus of the uterus, we have been able to collect only twelve genuine mesodermal tumors of the corpus acceptable by the pathologic criteria of Lawen.<sup>1</sup> There is much confusion in the literature concerning this tumor, and it is our object not only to establish its proper position, but also to throw light upon its nature.

The more important findings of these tumors have been classified in Table I. In the list of verified cases acceptable by the adopted diagnostic pathologic criteria described elsewhere, we have paid careful attention to the microscopic descriptions in each published case. All cases of pure rhabdomyoma or rhabdomyosarcoma of the uterus, such as those reported by Blair Bell<sup>2</sup> and Glynn, Lochrane,<sup>3</sup> and others, were rejected. The case of Wolfe<sup>4</sup> has been unacceptable. His tumor apparently presented all of the clinical and pathologic characteristics of a genuine mesodermal mixed tumor. Although the bulk of the tumor consisted of "nonstriated muscle cells intermingled with myxomatous tissue, osteoid and cartilage," a careful examination of the pathologic report of his case failed to reveal any true embryonal myoblasts. The absence of striated embryonic muscle cells so necessary for a pathologic diagnosis serves to eliminate those cases described as adenosarcoma by Sophian.<sup>5</sup> Simple tumors, such as osteoma, chondroma, etc., have not been included in this list.

The first case in the uterus was reported by Weber<sup>6</sup> in 1867. The tumor sprang from the cervix uteri of a multipara, 45 years of age, and revealed the characteristic microscopic structure of a mixed tumor. The first case of the body of the uterus was described by Anderson-Edmondson in 1870 and the second by Bystumoff-Eekert in 1874 (quoted by Kehrer).<sup>7</sup>

The area of osteomyelitis was demonstrated roentgenographically and its progressive spontaneous defervescence, revascularization, and healing was followed and similarly demonstrated. Several very small sequestra escaped or were removed from the wound during this period after which the very small sinus closed completely. The follow-up observation period is now sixteen months.

#### DISCUSSION

Although the local bone lesion in acute hematogenous osteomyelitis is a secondary matter to a bacteriemia originating from a primary lesion elsewhere (in this case a paronychia of one of the opposite toes), this case demonstrates conclusively that the local lesion itself in its turn can act as a local point of distribution for a secondary bacteriemia. A suggestive clinical point is that the secondary bacteriemia is usually of small magnitude, approximately under 25 colonies of bacteria to the cubic centimeters of blood cultured.

This type of bacteriemia is not influenced at all by chemotherapy with drugs of the sulfanilimide group. A bacteriemia of small magnitude continues because the thrombophlebitis keeps discharging bacteria into the circulation.

Under these conditions, clinicians should search carefully in the nearby veins for an accessible thrombophlebitis. Should such a thrombophlebitis be found, the indication becomes absolute to excise the affected segment of vein or to ligate it on the proximal side. In the absence of such demonstrable thrombophlebitis, the question of ligating the principal vein draining the affected area should be considered with due consideration to its feasibility anatomically and to any subsequent and consequent circulatory change.

All of this concerns itself only with the control of any bacteriemia which accompanies a focus of acute hematogenous osteomyelitis. The management of the bone focus itself should follow along well-established lines. My own very conservative viewpoints regarding the management of the local bone focus has been discussed very frequently and is marked by the most extreme conservatism as the management of the above described case shows.

In a personal communication, Dr. Champ Lyons, of the Massachusetts General Hospital, tells me that he also has recognized the importance of ligating the main tributary vein of the local bone focus as one of the items in his management of acute hematogenous osteomyelitis.

5. Herb, I. C.: Surg., Gynec. & Obst 10: 163, 1910.	55	Para m	Fundus, polypoid tumor filling the entire uter- ine cavity with much enlargement of the arteries	Embryonal striated muscle cells; cysts lined by epithelial cells	Onset 8 mo. before ad- mission with pelvic discomfort; watery and, at times, bloody vaginal discharge; menstruation; enlarged uterus; generalized pelvic tenderness	Supravag- inal hysterectomy	Regional recurrences with death 6 mo after operation
6. Nicholson, G. W.: Guy's Hosp Rep 69: 173, 1915	55	Para 1	Primary multicentric, multiple mesodermal mixed tumor of body of uterus	Embryonal skeletal muscle cells; smooth muscle; fat, cartilage; myomatous tissue; round and spindle celled sarcoma, carcinoma, carcino- sarcoma	Six months' history of pain in chest followed by dyspnea; loss of weight; hard tumor palpable just above symphysis pubis	None	Death 9 mo. after op- erated with multiple metastases to left pleura, lungs, liver, ovaries, and perito- neum of Douglas, pouch
7. Chavanne, M., and Nudel, P.: Case I La Gynecologie 19. 3, 1920.	50	Nono	Posterior wall of fun- dus; tumor the size and volume of a fetus at term, polypoid and nodular; irregular con- sistence; variegated color; invasion of interine cavity and my- ometrium	Embryonal muscle cells; sarcoma tissue, glands, car- tilage; osteoid tis- sue	Pelvic violent pains of 10 mo duration; pel- vic mass	Total hysterectomy	Death 15 mo after onset; clinical evi- dence of general- ized metastases in abdomen and dis- turbances of blad- der

TABLE I

REPORTED BY	AGE	PARITY	ORIGIN, SITE, CHARACTER	MICROSCOPIC FINDINGS	SYMPTOMS AND PHYSICAL SIGNS	TREATMENT	COURSE AND TERMINATION
1. Anderson, Edmonson, 1870. Quoted by Kehler, E.: Monatschr. f. Geburtsh. u. Gynäk. 23: 616, 1906.	50	None	Corpus uteri; large soft nodular tumor	Typical striated muscle; cystic glands; small mononucleated and large multinucleated cells	?	Hysterectomy	Death from hemorrhage
2. V. Frauché, O.: Ztschr. f. Geburtsh. u. Gynäk. 40: 183, 1899.	49	Parixi	Posterior wall of fundus and body; circular tumor size of a man's head filling the uterine cavity; polypoid and reddish white in color	Embryonal muscle cells; myxomatous tissue; sarcoma cells	Pelvic pains for 2 wk. before admission; marked anemia; fundal tumor discharging pus felt through dilated cervix	Total abdominal extirpation of uterus	Death 1 wk. after operation due to peritoneal metastases
3. Lawen, A.: Beitr. z. path. Anat. u. z. allg. Path. 38: 177, 1903.	60	?	Posterior wall of fundus of uterus; tumor about the size of a child's head; polypoid, soft, variegated brown to white in color	Embryonal striated muscle cells; glands; sarcomatous cells; hyalinized connective tissue; carcinomatous cells	Scanty postmenstrual vaginal bleeding for 6 mo.; uterus on admission was not enlarged	Vaginal hysterectomy	Local recurrences and peritoneal metastases (incomplete); death 11 mo. after onset with clinical picture of abdominal metastases
4. Hunziker, D. H.: Beitr. z. Geburtsh. u. Gynäk. 12: 317, 1907-08.	55	Parixii	Anterior wall of fundus; tumor mass round, polypoid, marmorated, grayish red, nodular and of very variable consistence; measurements, 6 by 4 by 5 cm.	Smooth and cross striated embryonal muscle cells; cartilage; myxomatous tissue; sarcomatous tissue; glands	Painless bloody vaginal discharge associated with increased frequency of urination to 6 wk. before admission; tumor about size of male fist palpated 1 fingerbreadth above symphysis; fundus reflexed	Total abdominal hysterectomy	Death 5 mo. after onset with local recurrences, abdominal metastases, and progressive emaciation

11. Gamper, A.: Arch. f. Gynäk. 129: 878, 1926-27.	54	Para viii	Corpus uteri; large polypoid deeply furrowed, waxy white mass broken up by multiple cavities	Embryonal striated muscle cells; cartilage; glandular; fibrillary connective tissue; myxomatous tissue; cysts filled with mucin	Yellowish white, blood-tinged vaginal discharge for 6 wk. before admission associated with intermittent slight pain over lower abdomen; upper pole of mass palpable three fingers above symphysis; corpus enlarged to about size of a fist; uterus freely movable	Hysterectomy	Patient still alive 4½ yr. after operation without evidence of metastases or local recurrences
12. Amolsch, A. L.: Am. J. Gynec. 37: 435, 1939.	57	Para x	Upper posterolateral wall of fundus; dilatation of uterine canal by a large soft, partially hemorrhagic polyp, microcystic, and containing an area of translucent cartilage; milary metastases in peritoneum and omentum observed at laparotomy; no autopsy	Rhabdomyoblasts; glands; cartilage and bone; myxomatous tissue; malignant polymorphous cell sarcoma	Postmenopausal vaginal bleeding of 3 mo. duration; polyp protruding through external cervical os, attached high in the uterine cavity; complaint of vaginal bleeding 2 yr. later	Complete hysterectomy	Death due to shock 1 day after operation

TABLE I—CONT'D

REPORTED BY	AGE	PART- ITY	ORIGIN, SITE, CHARACTER	MICROSCOPIC FINDINGS	SYMPTOMS AND PHYSICAL SIGNS	TREATMENT	COURSE AND TERMINATION
8. Chavannez, M., and Nadel, P.: Case II, La Gynecologie 19: 3, 1920	59	?	Posterior wall of corpus uteri greatly en- larged; tumor of ir- regular consistence; extensive invasion of myometrium	Embryonal muscle cells; cartilage; myxomatous and sarcomatous tissues; islands of squamous epithelial cells	?	?	?
9. Ritter, O.: Ztschr. f. Ge- burtsh. u. Gynäk. 89: 266, 1925-26.	58	?	Anterior wall of fundus; polypoid tumor, size of hen's egg, attached by a broad base; coarsely nodular; vari- egated color; invasion of myometrium	Embryonal muscle cells; myxomatous tissue; cystic glandular ocellu- sions; collagen	Vaginal bleeding for sev- eral weeks; physical signs (?)	Removal of uterus in- cluding cervix	No data
10. Haker, G.: Zentralbl. f. Gynäk. 50: 2191, 1926.	47	None	Posterior wall of corpus uteri enlarged, corre- sponding to a 5 mo. pregnancy; extension into cervical canal, portio vaginalis, and myometrium; no data as to color, consistence, etc.	Embryonal muscle cells; glands; myx- omatous tissue	Prolonged vaginal bleed- ing and foul smelling discharge; shortly be- fore admission, fre- quent vaginal passage of tissue fragments; physical examination revealed enlarged and freely movable uterus palpable at a level of two fingerbreadths be- low navel; vagina filled in part with ne- crotic, and in part with polypoid tumor masses.	Total ex- tirpation of uterus and adnexa	Alive and well with- out pelvic recur- rences 3 mo. after operation



*Subsequent Clinical Course.*—The patient remained well for six weeks, but thereafter complained of progressive weakness, anorexia, and loss of weight. She suffered from pain in the left chest. Examination revealed dullness and diminished breath sounds at the left base. Stereoscopic films at this time revealed "metastatic malignancy" involving both lung fields.

On June 11, 1938, the patient was readmitted to the hospital complaining of moderate interscapular pain and weakness. She appeared cachectic, but was mentally alert. The temperature ranged between 97.6 and 100° F., the pulse, between 80 to 110, and the respiratory rate, between 20 to 24. There was mottled dullness with diminished breath sounds throughout both lung fields, especially over the left upper anterior chest. No palpable masses were felt on abdominal examination. On June 14 the patient developed a complete paraplegia at the level of the twelfth thoracic vertebra and died four days later.

#### GROSS AND MICROSCOPIC DESCRIPTION OF SPECIMEN REMOVED AT OPERATION

*Gross Appearance of Primary Tumor in Uterus.*—The specimen consisted of a uterus and left oviduct and ovary removed at operation. The uterus was amputated above the cervix. It was roughly pyriform in shape and greatly enlarged, measuring 15 by 20 by 10 cm. in its diameters. Externally its surfaces were smooth and free from any gross abnormal changes of note. On sagittal section the entire wall appeared to be stretched by a large polypoid growth attached to both the anterior and posterior walls by a broad base. This contrasted with the botryoid tumors of the vagina which acquire their gross appearance principally because of the dominance of myxomatous tissue and the space for growth afforded by the vagina. Examination revealed that the entire uterine wall, including the endometrium, was replaced by tumor, and that the uterine cavity was much distended and filled with growth. The surface of the tumor was nodular and not lobulated. The consistence of the growth was generally firm. In color, the growth was predominantly pink to pinkish gray, and mottled with many irregular, soft, friable, opaque, yellow to yellowish brown areas up to 1 cm. in their widest diameter and a few small areas of fresh and old hemorrhage. There were frequent irregular, variably sized areas of smooth, translucent, grayish myxomatous tissue, and an occasional small, hard, irregular mass of bone. No grossly visible cysts were seen. There were no teratomatous structures and no tissues suggestive of cartilage.

The oviduct and ovary showed no gross changes worthy of note.

*Microscopic Appearance of Primary Tumor in Uterus.*—A large number of representative sections from different parts of the tumor and at various levels were prepared. These were fixed in formalin, Bouin's fluid, Heidenhain's "Susa" fluid, and absolute alcohol, and were stained with hematoxylin and erythrosin, van Gieson, Masson's iron hematoxylin, Mallory's acid fuchsin and aniline blue, Best's carmine for glycogen, Maximow's hematoxylin-eosinazure II for blood cells, Weigert-Pal for myelin sheaths, Bielschowsky-Plien for Nissl substance, Mayer's mucicarmine for mucin, and impregnated for axis cylinders according to the silver impregnation method of Bielschowsky-Agduhr.

An investigation of the recorded literature on the subject of vaginal, cervical, and corporeal mixed tumors indicates that the corpus uteri is definitely the least common site of their occurrence. These tumors more or less resemble certain other tumors of the type described by Wilms' as mixed tumors in the kidney and elsewhere. They are distinct from sarcomas, rhabdomyoma, and teratoma of the uterus. Their rarity, their remarkably varied structure, the clinical picture they present, and above all, the problems of histogenesis to which they give rise, make, together with a complete list of verified published cases, the recording of each new case an obligation.

#### CASE REPORT

Mrs M H, a 67 year old white, married, female, para iv, was referred to the Nathan Littauer Hospital on April 1, 1938, for removal of a large pelvic tumor.

*Present Illness*—The present illness began nine months before admission with dysuria and frequency of urination, progressive in character. Two months after the appearance of these urinary disturbances, the patient noticed enlargement of the lower abdomen. She complained at no time of pelvic pain, vaginal bleeding, discharge, or of any rectal disturbances. The presenting symptoms which forced her to seek medical advice were dysuria and frequency of urination.

*Family History*—Essentially negative.

*Past History*—The menstrual history was normal. Catamenia began at the age of 15 years. The menstrual periods occurred at regular intervals of twenty eight days with an average flow of seven days. Menstruation ceased suddenly at the age of 46 years, and there were no disturbing postmenstrual manifestations.

At the age of 42 years a thyroidectomy had been performed. At the age of 55 years the appendix, right tube, and ovary were removed, at which operation a small "uterine fibroid" was noted. Otherwise, the patient always enjoyed good health.

*Physical Examination*—The patient was a moderately nourished, elderly, white female, not acutely ill. The lower abdomen appeared moderately and uniformly enlarged. On abdominal palpation a fixed mass, indefinite in outline, occupying the suprapubic area and extending to the left, could be felt. In addition, moderate tenderness in the right lower quadrant of the abdomen was elicited. Pelvic examination revealed a multiparous introitus, a slight mucoid vaginal discharge, and no external evidences of infection. A mass, hard, fixed, smooth, and not tender, the size of a grapefruit, was felt in the region of the uterine body and appeared to extend into the left parametrium. The cervix was visualized and appeared normal. Otherwise, physical examination did not appear to be remarkable.

*Laboratory Data*—Urine. Specific gravity, 1.022, acid, 1+ albumin, negative sugar; and 2 to 3 WBC per high power field. Hematologic: Hgb (Newcomer), 78 per cent, RBC, 3,900,000, WBC, 10,100. Differential smear: polymorphonuclear leucocytes, 54 per cent, small lymphocytes, 34 per cent, large lymphocytes, 10 per cent, eosinophiles, 1 per cent, and basophils, 1 per cent, complement fixation and Kahn tests for syphilis, negative, sedimentation rate, 18 mm in one hour (Wintrobe), blood urea nitrogen, 17 mg. per cent, phenol-sulphonphthalein dye test, total dye excretion of 62 per cent in two hours.

*Treatment*—On April 4, 1938, laparotomy was performed under gas-oxygen ether anesthesia. A uterine mass, hard, smooth and fixed, filled the pelvic cavity and was attached to the sigmoid colon anteriorly and to a loop of ileum posteriorly. The right tube and ovary were absent. The left tube and ovary were normal. Examination of the contents of the abdominal cavity showed nothing unusual. A suprapubic hysterectomy and left salpingo-oophorectomy were performed. Cervical cancer was uneventful, and the patient was discharged on April 10, 1938.

strung closely together. As a rule, the cross striations were wholly absent or only partly to completely developed in the individual fibers. In the embryonal myoblasts sectioned transversely, the cross-striations were disposed concentrically in the perinuclear cytoplasm. They could be brought into sharp relief by peripheral degeneration in the latter. A definite sarcolemma was not observed. In a few cells paired centrioles were noted in the cytoplasm in close proximity to the nucleus.

The embryonal myoblasts commonly displayed a variable degree of degeneration (Fig. 2). Many of them were reduced to coarsely honey-combed and vacuolated cells with partial to complete loss of their longitudinal and cross-striations. The less severely damaged cells revealed swelling and separation of the longitudinal striations accompanied by karyorrhexis of the nuclei.

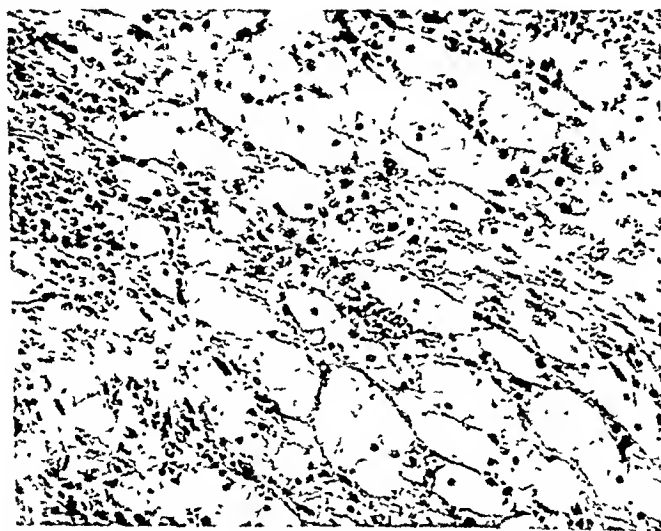


Fig 2.—Photomicrograph at  $\times 300$ , showing degenerated and necrotic embryonal myoblasts (hematoxylin and erythrosin stain).

In the sections stained for glycogen, the embryonal myoblasts commonly contained an abundance of glycogen granules indicative of their immature character.

No morphologic transition from embryonal myoblasts to normal adult smooth muscle cells could be traced.

*Smooth Muscle.*—Van Gieson preparations often reveal isolated strands and bundles of adult, normal appearing, fully differentiated smooth muscle cells.

*Glands.*—(Fig. 3.) Benign appearing glandular structures, strongly resembling normal endometrial glands of the uterine mucosa, were frequently incorporated within the substance of the tumor. Irregular in outline and dimensions and not surrounded by uterine stroma cells, they were lined by a single flat layer of medium to low columnar

The primary growth was composed of a wide variety of heterologous elements and structures among which the embryonal myoblast predominated and formed the essential matrix of the tumor. Only bone marrow and nerve tissue were conspicuous by their absence. Fresh and old hemorrhages into the substance of the tumor were frequent, and many small and large areas of partially to completely necrotized embryonal myoblasts were present.

*Embryonal Myoblasts.*—(Fig. 1.) These cells were irregularly laid down as variably sized solid islands and interlacing strands. Their individual variation in length and width was marked, ranging from  $10\ \mu$  to  $100\ \mu$  or more in length. The cells assumed a wide variety of shapes, appearing round, oval, triangular, pyriform, or even bizarre. Their nuclei varied considerably in size, shape, number, and even in

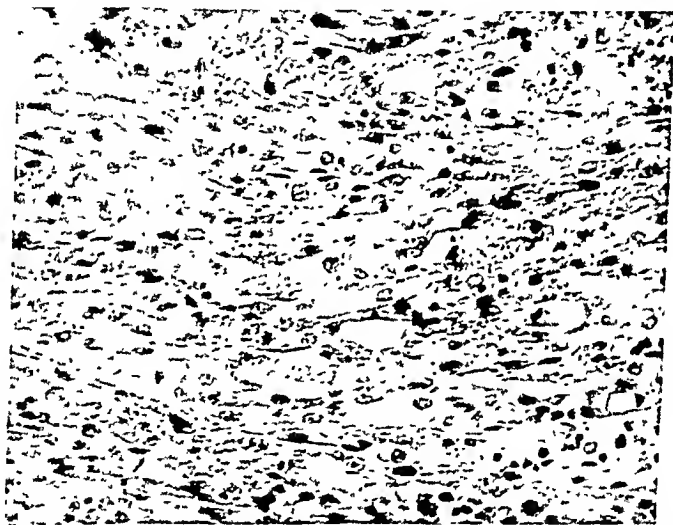


Fig. 1.—Photomicrograph at  $\times 375$  from section stained with van Gieson stain showing a field of embryonal myoblasts embedded in a vascularized myxomatous stroma.

chromatin content. However, the majority contained a single, relatively large, central or peripherally located nucleus with a prominent nucleolus, surrounded by a relatively sparse number of fine chromatin granules bounded by a densely staining nuclear membrane. The resemblance of the nucleus to that of a normal ganglion cell in the central nervous system was often striking. Many of the embryonal myoblasts were multinucleated, the nuclei often overlapping each other. Mitotic figures in different stages of development were relatively sparse in number.

The cytoplasm of the myoblasts was abundant and streamed out from the nuclear poles for a variable distance. These cytoplasmic processes did not fuse with each other to form a network.

Practically all of the cells revealed well-developed, delicate, longitudinal striations, consisting of fine bright red, fuchsinophile granules

strung closely together. As a rule, the cross striations were wholly absent or only partly to completely developed in the individual fibers. In the embryonal myoblasts sectioned transversely, the cross-striations were disposed concentrically in the perinuclear cytoplasm. They could be brought into sharp relief by peripheral degeneration in the latter. A definite sarcolemma was not observed. In a few cells paired centrioles were noted in the cytoplasm in close proximity to the nucleus.

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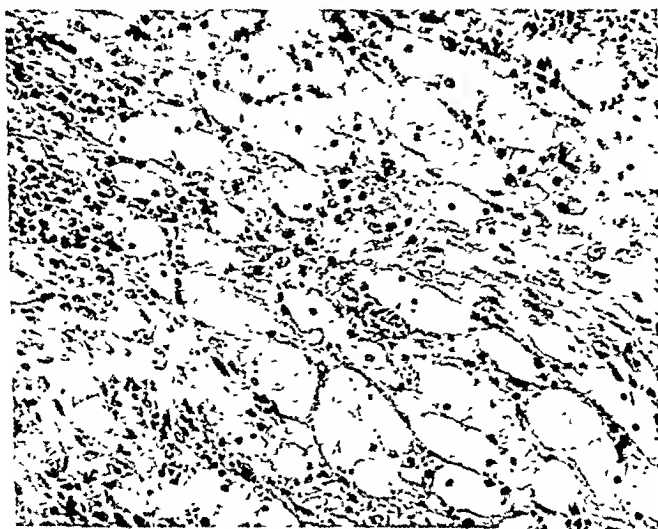


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epithelial cells. They revealed no morphologic evidence of secretory or menstrual activity or of malignant transformation.

*Myxomatous Tissue.*—(Fig. 4.) A striking feature of the tumor was the large number of irregularly distributed areas of mesenchymal myxomatous tissue. They consisted of triangular or stellate-shaped cell bodies from whose points passed long, delicate protoplasmic strands, forming a mesh network containing a slightly granular mucinous material stained pink in the Mayer mucicarmine preparations.

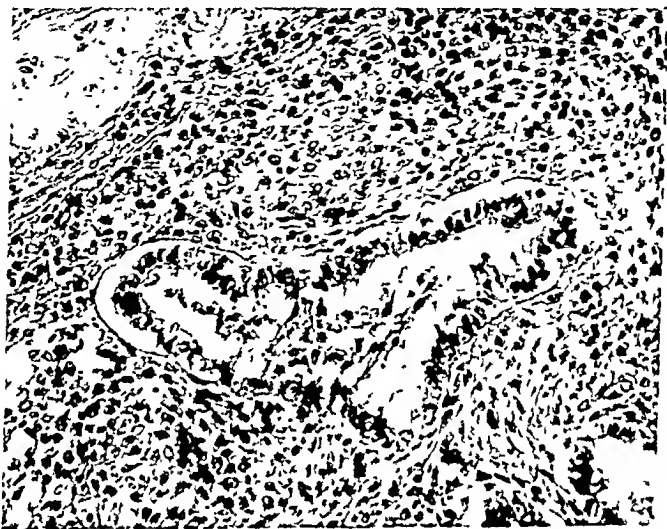


FIG. 3.—Photomicrograph at X280, showing a gland within the substance of the tumor resembling normal uterine endometrial gland and surrounded by embryonal myoblasts (hematoxylin and erythrosin stain).

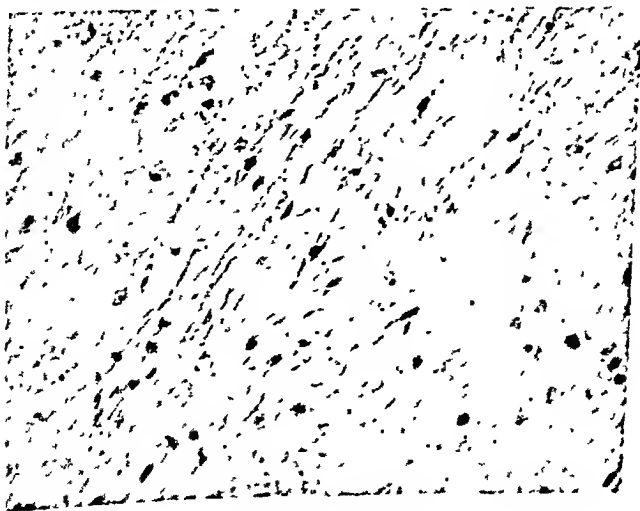


FIG. 4.—Photomicrograph at X375, showing in detail the myxomatous tissue (Mayer's mucicarmine stain).

*Adipose Tissue.*—(Fig. 5.) There were infrequent irregularly distributed nonencapsulated, small islands of adult nongranular fat cells, varied in size and shape.

*Collagen and Reticulum.*—There were many small areas and bundles of collagen, sparsely populated by nuclei. The Wilder silver preparations for reticulum showed a large number of wiry and stiff reticulum fibers.

*Cartilage.*—There were occasional islands of cartilage composed of more or less mature hyaline cartilage cells embedded in a pinkish red

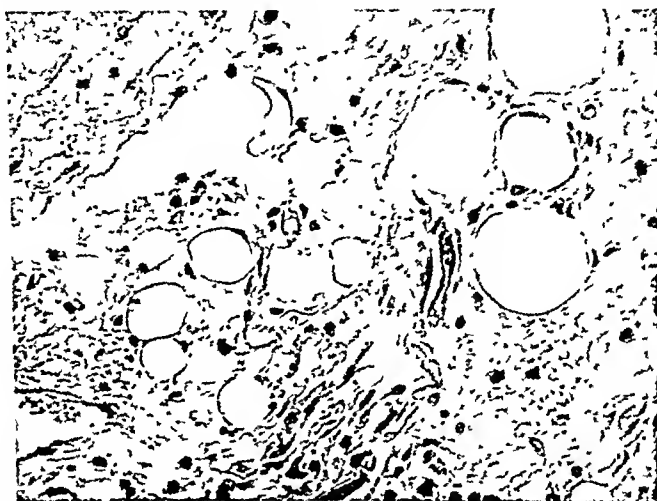


Fig. 5—Photomicrograph at  $\times 330$ , showing an area of adipose cells (hematoxylin and erythrosin stain).



Fig. 6—Photomicrograph at  $\times 220$  showing trabeculae of osteoid tissue (hematoxylin and erythrosin stain).

staining matrix and surrounded by a thin zone of spindle-shaped perichondrial cells.

*Bone.*—Adult osseous and osteoid tissue (Fig. 6) laid down as lamellae and without marrow cells between the latter was observed in only one area.

*Lymphatic Tissue.*—There were many foci of massed, small round cells unaecompanied by germinal or plasma cells. In the Maximow-stained preparations, the cells corresponded morphologically and tinctorially to normal adult lymphocytes. They were interpreted as such rather than as primitive mesenchymal cells.

*Nerve Tissue.*—A large number of sections stained for myelin sheaths and Nissl substance and impregnated with silver nitrate for axones failed to reveal any nerve tissue of any description.

*Blood Vessels.*—The tumor was, in general, richly vascularized by many new formed capillaries and veins. Clumps of characteristic embryonal myoblasts were not infrequently present in the lumina of the larger, thin-walled blood spaces. No other heterologous element was seen within them.

*Malignant Degeneration.*—There was no evidence of carcinomatous or sarcomatous degeneration.

#### AUTOPSY

Autopsy revealed a small, much emaciated, white female about 60 years of age. The peritoneal cavity contained a large metastasis over the left anterolateral portion of its wall. Smaller metastases were present over the anterior wall of the pelvic cavity and over the serosal coat of the large intestine. Each pleural cavity contained about 50 c.c. of a blood-tinged fluid, and its visceral and parietal surfaces were studded with many metastases, firm in consistence and predominantly opaque grayish white in color. The lungs and liver contained many scattered, round, metastatic nodules, measuring up to 6 cm. in diameter, and presenting a mottled yellowish red to opaque grayish white color. The lumbar lymph nodes were the seat of extensive neoplastic invasion.

No permission for examination of the spinal cord and vertebral column was granted.

Microscopically the metastases were composed only of embryonal myoblasts in a primitive stage of development. These were often present in the smaller veins of the lungs and liver.

#### REVIEW OF LITERATURE

*Terminology.*—The complex structure and composition of the heterotopic mesodermal tissue tumors of the uterus and vagina have given rise to an extremely complex nomenclature. McFarland<sup>2</sup> tabulated a list of no less than 116 terms employed to designate neoplasms which, on the basis of histogenesis and structure, may reasonably be grouped in one class. Often the presence of a dominant tissue element or of a



distinctive type of tissue has led to the confusing use of such terms as chondroma, myxoma, rhabdomyoma, etc. However, Lahm<sup>10</sup> groups the latter as simple tumors unless they are heterologous in nature or the one-sided development of a mesodermal mixed tumor.

McFarland has advocated the use of the term "dysontogenetic tumor" to designate this entire class of neoplasma developing in the urogenital system. This term is too broad in its scope and does not delimit the nature and behavior of the growth.

The term mesodermal mixed or combination tumor first proposed by Kehrer<sup>11</sup> and Meyer<sup>12</sup> is preferable to all others in that it is simple and indicates not only the complex morphologic structure of the growth, but also its relationship to displaced mesodermal embryonal rests. The use of the adjective mesodermal, as Meikle<sup>13</sup> points out, is desirable since it eliminates from this category teratomas containing derivatives of all three germinal layers.

The objection to the term *fibro-myxo-chondro-sarcoma* lies in its descriptive inadequacy. It suggests that only these elements are present, when, in point of fact, any single one may be absent in a given specimen. Furthermore, it fails to emphasize the presence of embryonal striated muscle cells essential for a pathologic diagnosis, as well as other structural elements.

The term *rhabdomyosarcoma* employed by Glynn and Blair Bell is satisfactory in one respect in that it indicates the presence of a very characteristic type of cell, the longitudinally and transversely fibrillated embryonal muscle cells. It also connotes the presence of sarcomatous tissue, which may be absent. However, as a descriptive name, it is too limited by virtue of its failure to indicate adequately the composite nature of the tumor. For these reasons it has been rejected.

Pfaannenstiel<sup>14</sup> employed the term *traubige Sarkom*, or botryoid sarcoma as it is known in this country and Great Britain, to describe graphically its grapelike character. This term is also unacceptable because a botryoid appearance is by no means always present in the mesodermal mixed tumors arising in the corpus of the uterus. On the contrary, the corpus tumor is almost invariably polypoid in character.

To conclude, it was decided after careful consideration of all the terms proposed to accept that of Kehrer as the most satisfactory in the present state of our knowledge; viz., mesodermal mixed tumor.

*Etiology.*—There is no clear proof that either age or parity is a factor of etiologic importance. Although the great majority of the cases occur in multiparas, there are insufficient data to draw any conclusions as to the etiologic significance of pregnancy. In addition, it is difficult to explain the average peak age incidence after menopause.

#### HISTOGENESIS

The occurrence, in an organ developed from the Müllerian ducts, of a neoplasm having tissue components of such wide variety has aroused

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which may be leveled not only at a Müllerian but also Wolffian duct origin is the dormaney of the cell rests for several decades. It is impossible, at present, to explain why these rests should slumber for years and then suddenly spring to life despite their association with many pregnancies and monthly ovarian cycles. Meikle has suggested that the cell rests are activated by hormonal disturbances but has offered no evidence as to their nature and behavior, and in point of fact, no proof of their actual existence. There is no demonstration that chronic irritation, constitutional predisposition, infection, etc., are growth stimuli. On the other hand, the strength of the Müllerian duct theory lies not only in the location of the tumor, but also in the pluripotential capacity for differentiation of the indifferent embryonal cells into myxomatous tissue, bone, etc. Additional support for this theory is offered by the rare presence of these tumors in the base of the urinary bladder. It is conceded that this theory is not wholly satisfactory, but it is the best offered so far.

There is much speculation as to which tissues or cells constitute the primitive matrix from which the other heterologous structures are derived. Wilms, Nicholson, and others believe that the embryonal myxomatous tissue is the matrix on the basis of morphologic evidence of a transition between this and other tissues. On the other hand, other students hold that groups of small round cells morphologically resembling lymphocytes represent the common mother tissue. The balance of evidence appears to favor an origin from embryonal myxomatous tissue.

#### COMPARISON OF MESODERMAL MIXED TUMOR OF CERVIX AND BODY OF UTERUS

Mixed tumors of the cervix are more frequently encountered than those of the corpus, the ratio being about 3:1. There is a striking difference in their age incidence. Tumors of the body occur most often about and after the climacteric, while those of the cervix almost always occur in women during the active sexual decades. Tumors of the vagina predominate in childhood and adolescence.

Both are clinically characterized by vaginal bleeding, foul leucorrhea, fulminating course, and a marked capacity for local recurrences. In microscopic structure they resemble each other closely, but differ from each other in gross appearance. The cervical tumor is almost invariably arborescent in character while that of the corpus is nearly always polypoid in type and possesses a distinct pedicle.

The diagnosis of cervical tumors can be made much earlier and with greater accuracy because of their earlier tendency to produce vaginal bleeding and their accessibility to inspection and biopsy. For these reasons they are not as apt to be confused with benign lesions as may often be the case with corporeal tumors.

much interest and speculation in its genesis. At present, there are two prevailing theories; viz., those of Pfannenstiel and Wilms.

Pfannenstiel has advanced the conception that the series of heterologous elements present in the tumor is derived from normal connective tissue of the uterine mucosa by a process of metaplasia initiated by some indeterminate cause. This theory has today but few adherents. Metaplasia can account for the development of smooth muscle, cartilage, and bone from mesenchymal tissue but not for striated muscle cells. A transition from normal, adult fibroblasts to striated muscle cells does not take place normally. Moreover, the transformation of smooth into striated muscle cells has never been proved. The presence of striated muscle cells is best attributed to an origin from a muscle anlage.

Nicholson<sup>15</sup> states that his case of multiple primary mesodermal mixed tumors can be best explained on the assumption of dedifferentiation and rejuvenation of the stroma of the uterine mucosa. Its cause is not known. It hardly seems reasonable that a physiologically and morphologically ripened tissue such as the stroma of the uterine mucosa can dedifferentiate into such diverse tissues as cartilage, muscle, etc.

Islands of fully differentiated striated muscle cells have been described by Gerode<sup>16</sup> and Nehr Korn<sup>17</sup> in the wall of two uteri removed after puerperal sepsis. These were not associated with a tumor. Mesodermal mixed tumors cannot be ascribed to their presence, although the striated muscle cells alone may well originate from them.

Wilms<sup>18</sup> has proposed a theory of origin based essentially upon Cohnheim's hypothesis of cell rests. He holds that the tumors spring from rudiments of primitive mesodermal tissue displaced and carried down from the lumbar region by the Wolffian body in its descent early in fetal life. This theory is supported by the complicated embryologic development of the genital tract favoring the deposit of cell rests and by the complex structure of the tumor. Careful analysis of all the evidence leads to the conclusion that cell rests originating from the Wolffian bodies are not the source of these tumors. Absence of striated muscle or of its anlage in the Wolffian system, as well as failure of these tumors to develop along the course of the Wolffian duct, controverts the Wilms' theory.

We agree with Mönekeberg,<sup>19</sup> Kehler, and Lahm that it is more probable that the cell rests arise from the Müllerian ducts after their fusion to form the uterus and vagina. Meyer<sup>20</sup> states that indifferent embryonal cell-rest displacements of the Müllerian ducts are probably very frequent in the region of the uterus and vagina and not rare even in the late months of fetal development. The rests are present chiefly in the deeper layers of the myometrium, especially in the anterior and posterior walls, early in fetal life. A valid objection to this theory is the absence of any proved cases of mixed tumors in the broad ligament or of any migration of the Müllerian ducts through them. Another objection

Gieson, the exact frequency of sarcomatous degeneration cannot be determined with accuracy.

*Microscopic Appearance.*—The microscopic structure of the tumor is relatively more characteristic and important than the gross changes. Only by careful microscopic examination of a large number of representative and suitably stained blocks of tissue is it possible to establish the true nature of the tumor. Although its structure is theoretically broad, and, therefore, extremely complex, all of the possible heterologous elements and tissue may not be present. Furthermore, extensive necrosis and hemorrhage often lead to their destruction and disappearance. Therefore, any single structure may be absent, but the presence of embryonal muscle cells is essential for pathologic diagnosis.

*Embryonal Myoblasts.*—These are present in various stages of development and in a variable number. Thus, in the cases of Gamper, Lawen, and our own, the bulk of the tumor consisted of embryonal striated muscle cells. The more primitive cells are spindle-shaped with a relatively large oval or ovoid single nucleus, vesicular in character, and frequently presenting mitotic figures. They do not constitute the stroma of the tumor but are an integral part of it. Unless stained with van Gieson's method, they may be rapidly confused with sarcomatous cells.

The larger and more fully developed cells are spindle-shaped or round, depending upon the plane of the section, and either long or short. They are arranged in groups or bundles. Their cytoplasm, which tapers to a blunt end, constantly presents a well-defined longitudinal fibrillation. A smaller number appear transversely fibrillated in part or in whole. With suitable stains the cytoplasm may show glycogen granules, a sign of their cellular immaturity as first pointed out by Marehand. The presence of fibrillation alone or associated with glycogen is an important cellular diagnostic criterion. The cells are either uni- or multinucleated. The nuclei are large, occupying the greater part of the cell, and characteristically vary in position. They appear irregular in outline and either vesicular or hyperchromatic. They show single or multiple mitotic figures. In view of their invasive properties, their presence in large numbers, especially within blood vessels, is a sign of grave omen.

*Smooth Muscle.*—Isolated strands or bundles of adult smooth muscle cells, staining a characteristic brownish yellow color with van Gieson's stain, are frequent.

*Myxomatous Tissue.*—This varies in amount and is morphologically characteristic. The cell bodies are stellate or triangular, with long protoplasmic strands streaming from their points to form a loose network containing a clear or slightly granular material. The nuclei of the cells are single and either round or oval.

GENERAL PATHOLOGIC DESCRIPTION OF MIXED TUMORS OF CORPUS  
OF UTERUS

*Macroscopic Appearance.*—Assuming that these tumors arise from cell rests of müllerian duct origin, the corporeal tumors, as would be expected, originate in the wall of the uterus, especially from the posterior wall of the corpus. They lead to a variable and generally globular enlargement of the uterus. The external surface of the uterus is usually smooth except, perhaps, for an occasional fibrous tag or subserous tumor nodule.

The volume of the tumor may attain considerable dimensions, reaching the size of an adult's head, and extending upward out of the pelvic cavity into the abdominal cavity to the level of the umbilicus or above. The tumor constantly bulges out into the uterine cavity, distending it for a variable degree.

In contrast to the well-known arborescent, grapelike form of the cervical type, corporeal tumors appear almost always as polypoid masses, projecting into the uterine cavity from a broad submucosal base. The tumor seldom presents itself as a solitary large polyp attached to the uterine wall by a pedicle.

The growth is usually submucous in location and is either sharply delimited or insensibly fused with the myometrium, which is replaced either in part or in whole by tumor tissue. The mucosa above its attachment is either variably thickened or completely destroyed by tumor as was the case with the tumor herein described. Commonly, the surface of the growth is covered with a variable number of polypoid excrescences.

As would be expected from their genesis, mixed tumors of the corpus reveal a marked variation in their macroscopic appearance, depending upon the number and relative proportions of their structural components. The cut surfaces are lobulated and a variegated and mottled red to brown to pink to grayish white in color, and appear translucent, gelatinous, opaque, and opalescent. Should the embryonal muscle tissue predominate, the color will be essentially grayish pink in color. Cartilage is only occasionally present in sufficiently large amounts to be identifiable as such. The consistence of the tumor is very variable, being very soft and friable in areas of necrosis, and dense and tough in others. Cystic cavities of variable dimensions, lined by rough, necrotic walls and filled with a bloody or foul smelling purulent fluid, are often present. They may be palpated as areas of distinct fluctuation. Areas of old and fresh hemorrhage are frequent. On section, bloody tissue juice may ooze.

Carcinomatous degeneration is extremely rare. A certain percentage has been described as containing areas of sarcoma, but the tumor does not grow properly, but the sarcoma is very ill defined, and after repeated sections embryonic myoblasts, fibroblasts, and other elements of sarcoma

formed, and the operative findings recorded in the literature are, as a rule, incomplete.

As with other malignant tumors, the mode of spread is largely governed by the aggressive nature of the tumor cells and by the texture and vascular and lymphatic richness of the stroma of the growth. Local extension into the uterus takes place essentially by infiltration of pre-existing or potential tissue spaces. The distant metastases are readily accounted for by venous invasion favored by the infiltrative destruction of the capillaries and veins, especially by the myoblasts. The lymphatics apparently play but a minor role as a channel of extension for local or distant metastases. There is no direct relationship between the extent and degree of the myometrial invasion and the number and distribution of the distant metastasis.

Despite the marked tendency to local invasion and postoperative local recurrences, the parametrium, bladder, and rectum are not invaded. Extension into the cervix with effacement of the cervical canal and deviation of the normal cervical axis has been observed only in the cases of Halter and Herb (Table I). Except for ovarian metastases in Nicholson's case, there is no other instance of invasion of the tubes or ovaries.

Although the lymphatics of the corpus uteri drain into the lumbar lymph nodes, metastases to them occurred only in our own case.

The pleurae, lungs, liver, and pelvic and abdominal peritoneum are the most common sites of remote metastases. In our own case, the pulmonary metastases were composed wholly of embryonal myoblasts.

#### PATHOLOGIC DIAGNOSIS AND PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF MESODERMAL MIXED TUMORS OF CORPUS UTERI

The microscopic diagnosis of these tumors should offer no difficulty provided that a large number of representative blocks of tissue differentially stained with van Gieson or with one of Masson's trichrome stains are carefully examined. The diagnosis can be established with certainty only by the demonstration of embryonal myoblasts in combination with one or more other heterologous elements such as myxomatous tissue, cartilage, glands, etc. The reason for the necessary presence of the embryonal myoblasts is that its presence can be accounted for only on the basis of an origin from displaced embryonal cells. Although essential for diagnosis, the mere presence of striated embryonal muscle cells alone does not warrant the diagnosis of mesodermal mixed tumor unless it can be shown that rhabdomyoma or rhabdomyosarcoma is a one-sided development of a mixed tumor. Their presence in association with heterologous elements serves not only to settle the diagnosis but also to eliminate such possible sources of confusion as corporeal carcinoma, endometrial polyp, fibroma undergoing ossification or cartilaginous changes, fibromyoma with or without calcification or occasional ossification, inflammation with diverse secondary metaplastic processes, chondromas, lipomas, etc.

the tumor is composed of a mass of small, round, uniform cells, which are arranged in a regular, cuboidal pattern. The cells are small, round, and uniform in size, and are arranged in a regular, cuboidal pattern. The cells are small, round, and uniform in size, and are arranged in a regular, cuboidal pattern. The cells are small, round, and uniform in size, and are arranged in a regular, cuboidal pattern.

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**Lymphocytes.** Multiple foci of small round cells, morphologically and functionally resembling lymphocytes, are often present.

**Squamous Cell Epithelium.** Occasionally, small islands of simple squamous epithelium may be seen.

**Columnar Epithelium.**—A columnar epithelial lining completely covering the tumor has been described, but this was not present in our own case despite the examination of a large number of tissue blocks taken from the surface of the tumor.

**Blood Vessels.**—Usually these tumors are richly vascularized by thin-walled blood vessels lined by a single layer of endothelial cells.

**Metastases and Local Recurrences.**—There is a definite tendency to simplification of the complex structure of the parent uterine tumor in the metastases and local recurrences so that the microscopic picture in the latter is more simple and uniform and dominated, as a rule, by embryonal myoblasts.

**Local Extension and Metastases.**—Although approaching chorion-epithelioma in its malignant behavior, it is not yet possible to indicate with accuracy the precise local and distant extensions of this tumor because of the lack of data. Only a few complete autopsies have been per-



formed, and the operative findings recorded in the literature are, as a rule, incomplete.

As with other malignant tumors, the mode of spread is largely governed by the aggressive nature of the tumor cells and by the texture and vascular and lymphatic richness of the stroma of the growth. Local extension into the uterus takes place essentially by infiltration of pre-existing or potential tissue spaces. The distant metastases are readily accounted for by venous invasion favored by the infiltrative destruction of the capillaries and veins, especially by the myoblasts. The lymphatics apparently play but a minor role as a channel of extension for local or distant metastases. There is no direct relationship between the extent and degree of the myometrial invasion and the number and distribution of the distant metastasis.

Despite the marked tendency to local invasion and postoperative local recurrences, the parametrium, bladder, and rectum are not invaded. Extension into the cervix with effacement of the cervical canal and deviation of the normal cervical axis has been observed only in the cases of Halter and Herb (Table I). Except for ovarian metastases in Nicholson's case, there is no other instance of invasion of the tubes or ovaries.

Although the lymphatics of the corpus uteri drain into the lumbar lymph nodes, metastases to them occurred only in our own case.

The pleurae, lungs, liver, and pelvic and abdominal peritoneum are the most common sites of remote metastases. In our own case, the pulmonary metastases were composed wholly of embryonal myoblasts.

#### PATHOLOGIC DIAGNOSIS AND PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF MESODERMAL MIXED TUMORS OF CORPUS UTERI

The microscopic diagnosis of these tumors should offer no difficulty provided that a large number of representative blocks of tissue differentially stained with van Gieson or with one of Masson's trichrome stains are carefully examined. The diagnosis can be established with certainty only by the demonstration of embryonal myoblasts in combination with one or more other heterologous elements such as myxomatous tissue, cartilage, glands, etc. The reason for the necessary presence of the embryonal myoblasts is that its presence can be accounted for only on the basis of an origin from displaced embryonal cells. Although essential for diagnosis, the mere presence of striated embryonal muscle cells alone does not warrant the diagnosis of mesodermal mixed tumor unless it can be shown that rhabdomyoma or rhabdomyosarcoma is a one-sided development of a mixed tumor. Their presence in association with heterologous elements serves not only to settle the diagnosis but also to eliminate such possible sources of confusion as corporeal carcinoma, endometrial polyp, fibroma undergoing ossification or cartilaginous changes, fibromyoma with or without calcification or occasional ossification, inflammation with diverse secondary metaplastic processes, chondromas, lipomas, etc.

The striated embryonal muscle cells in the absence of differential staining can be readily overlooked or confused with sarcomatous cells. An early tendency to degeneration and necrosis may obscure the microscopic picture and increase the chances of failure not only in detecting embryonal myoblasts but also other heterologous elements. Diagnostic curettage not only may fail to reveal the true nature of the tumor, but also may be actually misleading if the curette fails to scrape away a characteristic portion of the tumor.

A corporeal sarcoma, arising either in the *innocosa* or *myometrium*, especially if polypoid, grossly resembles a certain type of mesodermal mixed tumor of the corpus. The characteristic "raw pork" appearance in sarcoma described by Cullen should suggest the true nature of the tumor. However, despite the wide limits of variation of the cell structures of sarcoma, the combination of embryonal myoblasts and other constituent elements readily differentiates the two conditions. The occurrence of a sarcoma in a preexisting fibromyoma is diagnostically decisive in that there is no proved instance of such a development in mesodermal mixed tumor.

Mixed tumor is distinguished without difficulty from true teratoma of the uterus by the absence of rudimentary organlike masses of fetal tissues derived from all three germinal layers and present in a disorderly fashion.

Rhabdomyoma is rarely encountered as a tumor but occurs most commonly in or adjacent to the genitourinary system. Instances of this tumor have been described as arising in the uterus, vagina, and ovary. Both tumors contain embryonal myoblasts in various stages of differentiation, but the complex nature of mesodermal mixed tumors readily differentiates it from rhabdomyoma.

Abrikossoff's "*Myoblastenmyome*"<sup>26</sup> is another tumor which may be confused with mesodermal mixed tumor in that it arises from primitive embryonal myoblasts. The growth occurs most commonly in tissues and organs normally containing striated muscle cells, such as the tongue and voluntary musculature. However, it may arise in situations where striped muscle is not normally present. Therefore, its occurrence in the uterus is possible, although a careful search of the literature has failed to reveal any primary instances of this tumor in the uterus. Grossly, this tumor differs sharply from mesodermal mixed tumor, appearing as a small pale red or yellowish growth with or without areas of hemorrhage. The absence of longitudinal or transverse striations and of glycogen in the large and characteristically granular undifferentiated tumor cells of *myoblastenmyome* as well as of heterologous elements are decisive in differentiation.

#### SYMPTOMS

The symptomatology is essentially similar to that of corporeal carcinoma of the uterus. Postmenopausal bleeding and foul discharge

are the chief presenting symptoms. The hemorrhage may be profuse or slight. Frank bleeding is readily explained by the tendency to extensive necrosis and ulceration in a large tumor in which the vascular supply fails to keep pace with the rapidity of growth.

Pelvic distress and lower abdominal pain may occur but are usually late in appearance. They are varied in character, being either slight or severe, intermittent or continuous.

In contrast to cervical cancer, symptoms referable to hydronephrosis and pyonephrosis do not occur. Compression of the ureters by the tumor or actual invasion of the bladder did not occur in our case and has not been described. This may be due to the fulminating malignant character of the tumor, so that insufficient time elapsed for the development of these complications. In point of fact, urinary symptoms, such as dysuria and increased frequency, are not the rule. A review of the literature failed to reveal any symptoms attributable to pressure upon the rectum.

There are a marked anemia, cachexia, and debility in the terminal stages of the disease.

#### PHYSICAL SIGNS

The growth is centrally located in the uterus, usually regular and rounded in contour, and in consistence is comparable, as a rule, to that of a fibromyoma. If large, it is readily felt on abdominal palpation and may even be palpated at or above the level of the umbilicus. Most frequently the mass is freely movable because of its tendency not to invade the parametria. Since there is rarely invasion of the adnexa, no masses are felt in the fornices. The growth may project through the cervical canal and even into the vagina as a friable, broken-down mass. In von Franqué's<sup>22</sup> case a tumor the size of a man's head was felt through the dilated cervix as a soft, polypoid mass, in part degenerated, and discharging a yellowish, purulent secretion. Again in Halter's case the vagina was filled in part with a necrotic mass and in part with polypoid tumor masses.

On examination the findings most characteristic of a mixed tumor of the corpus uteri are its large, smooth, rounded contour, and absence of fixation.

#### CLINICAL DIAGNOSIS

The accurate clinical diagnosis of the disease is impossible because of the origin of the growth in the myometrium, so that curettage in the early stage is not likely to reveal changes indicative of the lesion. The tumor must be distinguished primarily from the more common post-menopausal causes of vaginal bleeding and discharge, such as carcinoma of the corpus and cervix uteri, sarcoma, myoma with secondary sarcomatous development, and granulosa-cell carcinoma. The most confusing condition in the clinical differential diagnosis is corporeal car-

cinoma of the uterus. At best an endometrial mixed tumor can be suspected on the basis of a rapidly growing, freely bleeding, smooth, large, definitely demarcated, postmenopausal fundal tumor. Both develop typically after menopause and their clinical pictures resemble each other except for the difference in the rapidity of their course. The final differentiation of the two conditions rests upon a careful examination of a large number of representative and suitably stained sections.

It is highly doubtful whether visual observation of the tumor projecting into the vagina would lead to correct diagnosis.

#### COURSE AND PROGNOSIS

The prognosis is uniformly unfavorable, rivaling that of chorion-epithelioma. Apart from a certain percentage of deaths occurring after operation, all of the verified cases succumbed within six to twelve months or less after the onset of the initial symptoms regardless of the type of treatment instituted. The only single exception was the patient of Gamber,<sup>23</sup> who survived four and one-half years at date of publication in 1926. There are no five-year cures.

Although the evidence is still inadequate, it would appear from our own case and from those of L  wen and a few others that a preponderance of embryonal myoblasts in the primary growth is an unfavorable sign in view of the propensity of these cells to produce metastases.

Most of the patients have died in a state of malignant anemia and cachexia due to local pelvic recurrences and remote metastases to the liver and lungs.

#### TREATMENT

If it has been shown with reasonable certainty that remote metastases have not developed, removal of both tubes and ovaries and the entire uterus is indicated. This is warranted by the gravity of the disease, the early invasion of the blood stream, and the speed with which it leads to a fatal termination.

Radical pelvic surgery should be followed by a course of deep x-ray therapy. The law of Bergonie and Tribondeau<sup>24</sup> states that the radiosensitivity of a tissue is proportional to its reproductive capacity and inversely proportional to its degree of differentiation. Scott<sup>25</sup> has furnished ample evidence to show that radioresistance increases with the change from the embryonal to the adult state. The most spectacularly sensitive growths are Wilms' tumor of the kidneys, seminoma of the testicle, lymphoepithelioma of Schminke, embryonal carcinoma of the ovary, and lymphosarcoma. Inasmuch as the myoblasts usually form the bulk of the tumor and are embryonic, undifferentiated cells, post-operative deep x-ray therapy is worthy of a trial. There are no cases on record cured for a five-year period by radium or deep x-ray therapy alone.

## SUMMARY

Cases of mesodermal mixed tumors of the body of the uterus were collected from the literature and were critically analyzed. An additional case of our own has been described. In the light of present evidence, an origin from embryonal cell rests of the müllerian duct appears to be the most acceptable today but is not completely satisfactory.

This group of tumors has been demarcated from other complex tumors of the uterus, such as teratoma, rhabdomyoblastoma, complex sarcomas, etc., by the adoption of certain pathologic criteria. The necessity of the presence of embryonal myoblasts in association with one or more heterologous elements for pathologic diagnosis was emphasized. Attention has been drawn to the grave prognostic significance of a predominance of embryonal myoblasts in the primary growth due to their propensity in invading the blood stream.

The clinical picture of these tumors is described. Due to early extension into the blood stream, complete removal of the uterus and its appendages is indicated. Postoperative deep x-ray therapy is worthy of a trial because of the essentially embryonal character of the tumor. No five-year cures have been reported in the literature.

We are indebted to Dr. John A. Sampson, of Albany, N. Y., for his helpful criticisms and suggestions.

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# NONTRAUMATIC INTRACEREBRAL HEMORRHAGE WITH CLOT FORMATION

## A REPORT OF SIX OPERATIVE CASES

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THE incidence of subcortical hemorrhage with clot formation without history of trauma seems relatively low. Either this is due to lack of recognition of the syndrome or to the actual infrequency of the condition. The etiology of this syndrome continues to be a subject of much controversy. Because of these factors, I feel that it is pertinent to report six cases of nontraumatic subcortical hemorrhage with clot formation and to review the literature.

### ETIOLOGY

Charcot and Bouchard<sup>1</sup> introduced the theory, and adduced evidence from cases, that such hemorrhage was the direct result of the rupture of miliary aneurysms. This theory prevailed in textbooks and writings on the subject for many years. Globus and Strauss,<sup>2</sup> in 1927, reviewed the literature and came to somewhat different conclusions. They stated, from their own experience, the belief that spontaneous intracerebral bleeding was the consequence of (1) an area of softening about an arteriosclerotic vessel and (2) hemorrhage from the previously weakened vessel. They believed, along with many of the older pathologists, that the hemorrhage is the result of rupture of a diseased blood vessel which may or may not have aneurysmal dilatation. These two theories have numerous adherents. Neither theory, however, will explain the occurrence of spontaneous intracerebral bleeding in every patient, both young and old. Intracerebral bleeding with clot formation has been a common autopsy finding and subsequent search has often failed to reveal the expected aneurysmal dilation of an intracerebral vessel. Moreover, softening of brain tissue about blood vessels can hardly be given as a cause of intracerebral bleeding in a young individual without primary general or localized arteriosclerosis.

### CASES FROM LITERATURE

Few neurosurgeons have had the temerity to consider operation advisable in patients with evidence of spontaneous intracerebral hemorrhage. Some of these patients are often very poor operative risks and operation would indeed be but a feeble gesture. There are some instances, however, where operative procedures are definitely indicated. There have been sporadic reports from the literature from time

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to time of operative intervention with some degree of success in localized intracerebral bleeding. I have collected seventeen cases in which there has been operative intervention, cases of spontaneous bleeding into cerebral tumors, rupture of lenticulostriate artery, middle meningeal hemorrhage; instances of post-traumatic bleeding are not included (Table I).

TABLE I

DATE	SEX	PRE- OPERATIVE DIAGNOSIS	SURGEON	AGE	DURATION OF SYMPTOMS	OPERATIVE RESULT
1903	M		Cushing <sup>8</sup>	40	36 hr.	Death, pneumonia 2 days
1906		Hemorrhage	Spiller <sup>7</sup>	40	6 wk.	Death
1922	M	Tumor	Adson and Craig <sup>4</sup>	37	6 wk.	Recovery
1929	F	Tumor	Adson and Craig	20	6 wk.	Recovery; death 3 mo., <i>Streptococcus</i> <i>viridans</i>
1932	M	Tumor	Adson and Craig	25	13 days	Recovery
1932	F	Tumor	Adson and Craig	30	5 wk.	Recovery
1934	M	Tumor	Adson and Craig	46	10 days	Recovery
1934	M	Tumor	Adson and Craig	35	6 wk.	Death on ninth post- operative day
1932	F	Tumor	Bagley <sup>3</sup>	48	22 mo.	Death, hemorrhage into cavity
1932	F		Bagley	39	5 hr.	Death, 10 days, pneumonia
1932	M		Bagley	49	6 mo.	Death
1932	M		Bagley	43	6 mo.	Recovery
1932	M		Bagley	35	1 hr.	Recovery
1922	F		Andre-Thomas, Schaeffer, de Martel, and Guillaume <sup>10</sup>	37	2 mo.	Recovery
1927	F	Tumor	Krone and Mintz <sup>6</sup>	54		Recovery
1933	M	Hemorrhage	Penfield <sup>9</sup>	14	5 days	Recovery
1933	F	Hemorrhage	Penfield	40	6 days	Recovery; sudden death 6 mo. later

From a study of these cases certain things are apparent. Eight of these 17 cases were operated upon with diagnosis of intracranial neoplasm. Five of the 6 operative cases which I am adding to this number were likewise operated upon with a diagnosis of brain tumor. The ages ranged from 14 to 54 years. Duration of symptoms previous to time of operation ranged from one hour to six months.

Spiller,<sup>7</sup> in 1908, stated that the duration of life of patients with hemorrhage into the brain ranged from five hours to two months. The cases listed above show this to be definitely on the pessimistic side. Of these 17 cases, there were 11 operative recoveries. Cushing's<sup>8</sup> case, in 1903, died of pneumonia on the second day. Penfield's<sup>9</sup> second case, reported in 1933, died suddenly six months postoperatively; post-mortem was refused. One of Adson and Craig's cases, operated upon in 1929, died of *Streptococcus viridans* three months postoperatively; post-mortem was refused. In Bagley's series there were 3 operative deaths, 1 with hemorrhage into the cavity after evacuation of the clot, 1 with pneumonia after ten days; post-mortem was refused on the third case. In Spiller's case, reported in 1906, the patient died shortly after operation. These results would lead one to believe that, in certain carefully selected cases, operation might be the treatment of choice rather than the more or less watchful waiting of other years. The period of time elapsed from onset of symptoms to the operation, in the above cases, where a fatality resulted, ranged from thirty-six hours to six months. In those sustaining operative recovery, the time elapsed varied from one hour to six months. Time elapsed from onset of symptoms would thus not appear to be a good criterion as to whether or not operative intervention would be successful. The age of the patient would likewise appear to have little bearing on the outcome. The average age of the recovered cases and those who died was approximately the same. Furthermore, the percentage of recovery, with ultimate favorable prognosis, would seem actually to make one more enthusiastic than many a similar series of patients operated upon with a diagnosis of brain tumor.

#### ANALYSIS OF CASES, INCLUDING 6 CASES BEING REPORTED

A study of the symptoms and signs exhibited by these 23 patients is interesting and informative (Table II).

Headache and unilateral motor weakness were the predominating symptoms, being present in 20 and 21 instances, respectively. The blood pressure was elevated in only 6 instances. Convulsions were exhibited by 2 patients. Choked disks were present 14 times. Five patients had a hemianopsia, the lesions in these cases being distributed about evenly between the temporal and occipital areas. Aphasias were present in 4 instances and pyramidal tract signs in 13.

The lesions were distributed as follows: temporal, 14; occipital, 3; frontal, 4; temporal-parietal, 1; cerebellar, 1.

I have operated upon the last 6 cases included above with 5 operative recoveries and with a satisfactory clinical result in each case.

#### CASE REPORTS

CASE 1.—K. K., aged 17 years, was admitted to St. Luke's Hospital on Oct. 19, 1935, with a chief complaint of headache, blindness, nausea, and vomiting of one week's duration. One week before entering the hospital, he noted a sharp con-



TABLE II

DATE	HEAD-ACHE	WEAK-NESS	EYE SIGNS	FOCAL SIGNS	LESION	BLOOD PRES-SURE
1903	Absent	Left	Choked disks	Difficult speech	Left temporal	300
1906	Absent	Right	Choked disks; homonym- ous hemi- anopsia	Right hemiple- gia	Left temporal	
1933	Present	Right	Choked disks	Difficult speech	Left frontal	110
1929	Present	Left	Choked disks		Right temporal	105
1932	Present		Homonymous hemianopsia	Aphasia	Left temporal	110
1932	Present	Right	Ptosis right	Right hemiple- gia; right seventh	Left temporal; parietal	100
1934	Present	Left			Right frontal	125
1934	Present	Left	Choked disks		Left frontal	110
1932	Present	Right	Choked disks	Right hemiple- gia	Left temporal	200
1932	Present	Right	Choked disks	Right hemiple- gia	Left temporal	220
1932	Present	Right		Right hemiple- gia	Left temporal	210
1932	Present	Right	Choked disks; homonym- ous hemi- anopsia		Left temporal	120
1932	Present	Right	Choked disks	Right hemiple- gia	Left temporal	160
1932	Present	Left	Choked disks	Left hemiple- gia	Right temporal	
1927	Present			Central right seventh	Cerebellar	120
1933	Present	Right		Hemiplegia right Aphasia	Left temporal	
1933	Present	Right	Choked disks	Aphasia	Left temporal	
1935*(1)	Present	Left	Choked disks	Left Babinski and Oppen- heim	Right occipital	116
1935*(2)	Present		Altitudinal hemianopsia		Right occipital	120
1936*(3)	Present	Left		Left Babinski; reflexes in- creased	Right temporal	118 86
1938*(4)	Present	Left	Homonymous hemianop- sia; choked disks	Left Babinski; ankle clonus; absent ab- dominals	Right occipital	110
1935*(5)	Present	Left arm		KK and AJ Left > right	Right frontal	140
1940*(6)	Present	Right	Early choked disks	Right Babin- ski; reflexes hypoactive	Left temporal	108 74

\*Author's cases.

tinuous pain over his right eye. One hour later he suddenly became blind. Vomiting, projectile in type, began shortly thereafter. He was taken home from school and was seen by his physician. Two days later he was seen in consultation at another hospital in the city; operation was advised and refused, as he seemed to be improving. Two days before entry to St. Luke's Hospital the patient noted some return of light perception but could not see definite objects. Physical examination showed: temperature, 99.2°; pulse, 66; respiration, 24; and blood pressure, 116/58. The remainder of the physical examination was negative. Neurologic examination revealed the left pupil larger than the right, both reacting to light and accommodation. Examination of the fundi revealed bilateral choked disks. There was slight

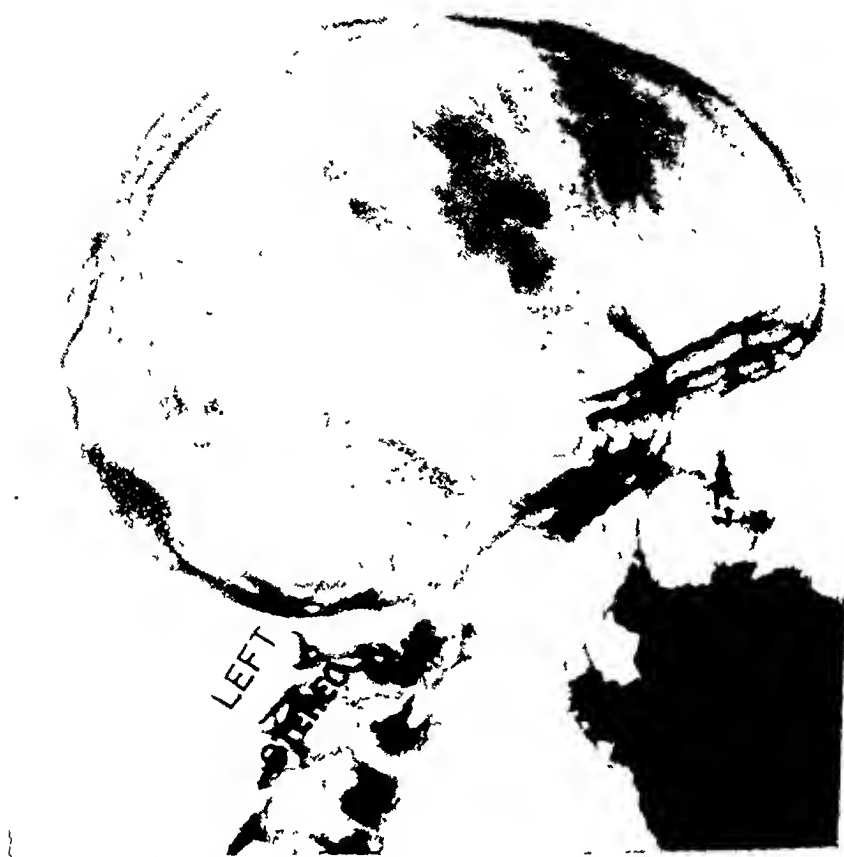


Fig 1—Case 1 (K K) Air was injected into lesion in right occipital region.

motor weakness of the entire left side without disturbance of sensation. Babinski and Oppenheim were present on the left. The other reflexes were not remarkable. A ventriculogram was done on Oct. 21, 1945, and a lesion demonstrated in the right occipital lobe (Figs. 1 and 2). On the following day a craniotomy was done, a right occipital flap being turned. A small greenish blue area was found on the cortex of the right occipital lobe. A small incision was made through this area with the electrosurgical knife. An organized clot about the size of a lemon was then uncovered and evacuated with suction. Bleeding was controlled and the bone flap replaced. The cavity was filled with Ringer's solution and the wound closed without

drainage. Convalescence was uneventful and he left the hospital seventeen days after entry. There was a residual left homonymous hemianopsia which has gradually, though not entirely, cleared.

CASE 2.—C. B., aged 65 years, was admitted to St. Luke's Hospital on Nov. 24, 1935, with a chief complaint of blindness of three months' duration. On the morning of Aug. 10, 1935, the patient awakened and was unable to see. After about two weeks his vision slowly returned. Two weeks before entry and two and one-half months after the original attack, he had another episode, resulting in total blindness. For the two weeks preceding hospital entry, light perception only was present. There was no paralysis, vertigo, vomiting, or feeling of illness. Physical examination was negative throughout. The blood pressure was 120/90. Neurologic examination



Fig. 2.—Case 1 (K. K.). Anteroposterior view of patient shown in Fig. 1.

revealed an altitudinal hemianopsia without papilledema. There was no sensory or motor weakness. Reflexes were normal throughout, except that there were absent abdominal reflexes on the right. A ventriculogram was done on Nov. 29, 1935 (Figs. 3 and 4), at which time a right occipital lobe lesion was demonstrated. On Dec. 3, 1935, a right occipital flap was turned and a large subcortical clot about the size of a tennis ball along with some brain cortex was removed. The center of the clot contained about 70 c.c. of fluid. The wound was closed without drainage. The patient left the hospital on the eleventh post-operative day. When last contacted on Dec. 15, 1936, this patient was doing very nicely. He had a slight residual left homonymous hemianopsia.

CASE 3.—M. C., aged 32 years, was admitted to St. Luke's Hospital on March 23, 1936, with chief complaint of headache, paralysis of left arm, and paresis of the left leg of two and one-half years' duration. Two and one half years before entry the patient noticed a sensation of numbness in thigh on the left. A few days later her left leg became paralyzed and she began to have jerking movements of the left leg and arm. Three months before entry these convulsions became more frequent. During this time, she began having headaches of a very severe nature. She noted blurring of vision and vomited on a few occasions. Past history was not remarkable. Physical examination showed: temperature, 98.6°; pulse, 100; respiration, 24; blood pressure, 118/86. Neurologic examination showed cranial nerves intact

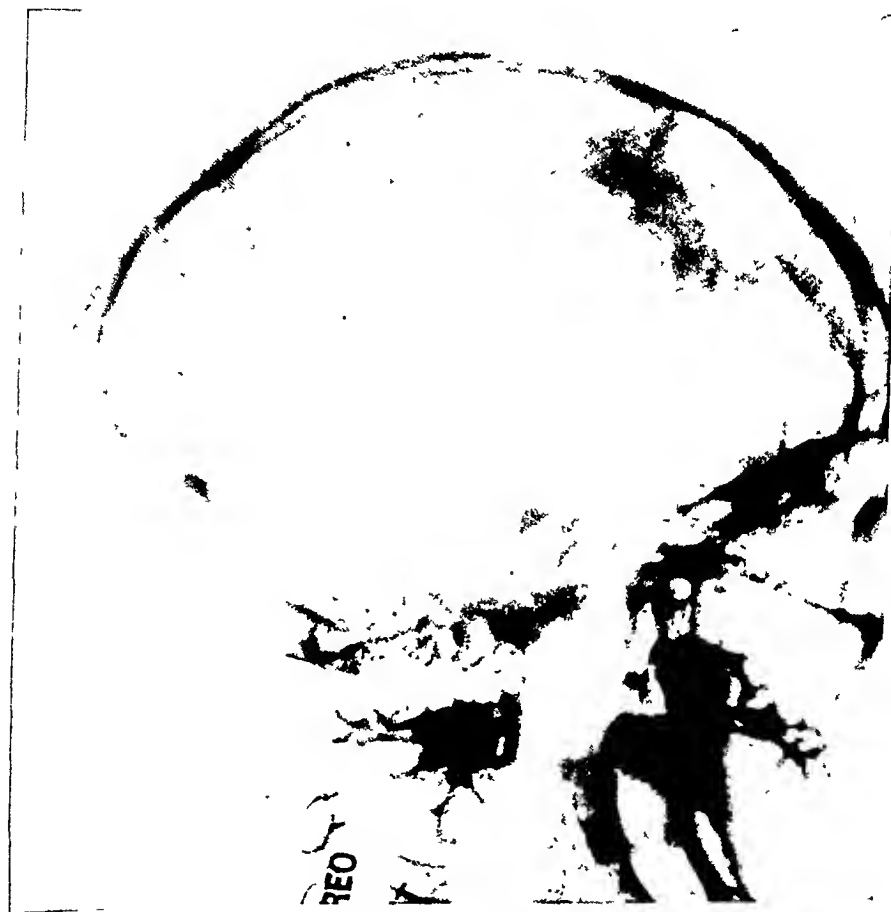


Fig. 3.—Case 2 (C. B.). Lateral view, showing lesion in right occipital lobe.

and marked motor weakness of the extremities on the left. There was no spasticity. There was no Babinski reflex, an ankle clonus, and slight increase of reflexes on the left. Visual fields were normal. An encephalogram was done on March 26, 1936, and showed xanthochromic fluid without visualization of the ventricles. On March 30, 1936, an exploratory craniotomy was done. A right temporal parietal flap was turned and, in attempting a ventricular puncture, a large cyst was encountered. The cortex was incised behind the motor area and the region of the arm center and about four ounces of old blood and clots were removed. A small piece of tissue was removed for microscopic examination. The wound was closed in the usual manner

without drainage. The patient had an uneventful postoperative course. Examination of the specimen microscopically revealed arteriosclerosis with hemorrhage and brain softening. The patient was discharged on April 12, 1936. She was walking fairly well with some residual spasticity of left arm and leg. She was last seen by us on July 26, 1936.

CASE 4.—W. S., aged 11 years, was admitted to Deaconess Hospital on Oct. 3, 1938, with the chief complaints of blurring of vision, loss of the lateral field of vision on the left, dizziness, nausea, and vomiting. Two days previous to hospital admission the patient had had a severe headache, followed by marked nausea and vomiting, blurring of vision, and loss of the lateral field of vision, and these persisted until admission to the hospital. There was no history of trauma. Physical examination was negative throughout. The blood pressure was 110/60. Neurologic examination revealed bilateral choked disks, left facial weakness, absent abdominal and cremasteric reflexes on the left, and hyperactive reflexes on the whole left side. There was a left Babinski and a suggestive ankle clonus. Examination of the visual fields revealed a left homonymous hemianopsia. A ventriculogram was done on Oct. 4, 1938.



Fig 1—Case 2 (C. B.). Posteroanterior view, demonstrating dilated right lateral ventricle.

A lesion was demonstrated in the right occipital lobe and an occipital flap was turned. A large subcortical clot was discovered in the occipital lobe. Because the brain had the appearance of tumor, a large portion of the occipital lobe was resected. A decompression was done and the wound was closed in the usual manner without drainage. The postoperative course was uneventful. Microscopic sections of excised portion of the occipital lobe showed no evidence of tumor. The patient was discharged from hospital Oct. 19, 1938. This patient has returned to his normal activities. He has a slight residual left homonymous hemianopsia.


 A high-contrast, black and white posteroanterior radiograph of a human skull. The image shows the internal table of the skull with a prominent, dark, irregularly shaped area in the central region, indicating a depressed and shifted ventricular system. The word "RIGHT" is printed in bold, capital letters on the left side of the image, near the base of the skull.
 

RIGHT

Fig 5—Case 5 (J. C.) Posteroanterior view Ventricular system depressed and shifted to left

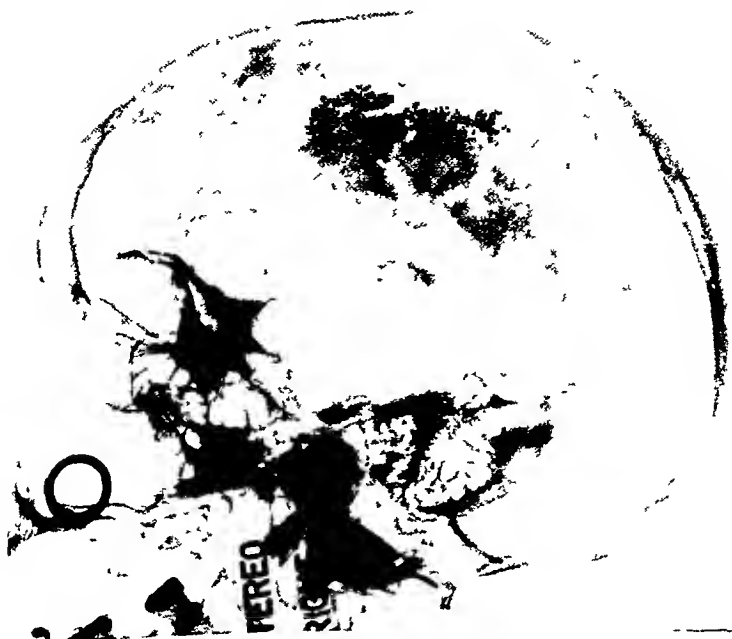


Fig 6—Case 5 (J. C.) Lateral view Right lateral ventricle compressed, anterior portion depressed Reduction in capacity of whole ventricle.

CASE 5.—J. C., aged 50 years, was admitted to St. Luke's Hospital on March 11, 1940, with a chief complaint of recurrent headaches of several years' duration. About six years before the present hospital entry, she was studied at another hospital because of severe recurrent headaches. She had had migraine attacks since early youth, several of these attacks requiring hospitalization. The present attack began on the evening of Feb. 28, 1940, with very severe headache, nausea, vomiting, cramps in the legs, and pain in the chest. Physical examination, at that time, revealed a somewhat lethargic woman of 50 years of age, apparently quite weak and complaining of right temporal headache. The blood pressure was 140/100. Physical examination was otherwise not remarkable. Neurologic examination showed normal fundi and slight hyperactivity of knee jerks and ankle jerks on the left. There was



Fig. 7 —Case 6 (M. K.). Left lateral view. Filling defect in left lateral ventricle in parietal temporal region.

no Babinski. The left arm seemed weaker than the right. The patient was observed for several days. However, by March 10, 1940, the date before admission to the hospital, the patient had become disoriented, inactive, and stuporous. The left arm was weaker than the right. There was suggestive facial weakness on the left. The reflexes in the left arm and leg were more active than on the right. The pulse was 52, the blood pressure, 150/90. On March 11, 1940, a ventriculogram was done (Figs. 5 and 6) which demonstrated a definite lesion in the right frontal area. A right frontal flap was turned. An enormous subdural hematoma extending from the parietal lobe to the tip of the frontal lobe was removed with a suction tip. This exposed an area of clot protruding through the tip of the frontal lobe. When

tho clot was removed, there was a gush of old black blood from the subcortical area of the frontal lobe. Because of the fact that the frontal lobe gave the appearance of tumor, a right frontal lobectomy was done with removal of the frontal lobe anterior to the motor cortex. The wound was closed in the usual manner without drainage. The patient left the hospital on April 13, 1940, after a somewhat prolonged convalescence. This patient is now able to be up and about her home and is gradually regaining use of her left arm.

CASE 6.—M. K., aged 30 years, was admitted to St. Luke's Hospital on Aug. 6, 1940, with a chief complaint of paralysis of the right side of four days' duration. Four days before entry to the hospital, the patient had a gastrointestinal upset, consisting of nausea, vomiting, and diarrhea. He slept well that night and arose as usual the following morning. About 10 A.M. the mother found him lying on his bed in a stuporous condition, unable to talk or to move his right side. This condition



Fig. 8.—Case 6 (M. K.). Posteroanterior view. Entire ventricular system shifted to right.

continued without change until entry to the hospital. Physical examination showed: blood pressure, 108/74; temperature, normal; pulse, 54; respiration, 20. Neurologic examination showed a right central facial paralysis; the fundi were negative upon admission, but within three days had developed a slight hemorrhage about the left optic disk. There was some anesthesia of the face on the right and complete paralysis of the right hand and foot. The reflexes were decreased on right side and there was a right Babinski. There was a motor and sensory aphasia. Visual fields could not be obtained. It was thought the patient had a subcortical clot on the left side. On Aug. 8, 1940, a ventriculogram was done (Figs. 7 and 8), demonstrating a lesion in the left temporal parietal area. On Aug. 10, 1940, a left temporal parietal flap was turned in the usual manner. A needle was inserted behind the



Rolandic artery and above the Sylvian fissure to a depth of 5 cm., where a blood clot was encountered. The cortex was then split and a large clot exposed and removed with suction. Bleeding points were coagulated; the wound was closed without drainage. The patient's postoperative course was entirely normal for the first twenty-four hours, but he died suddenly on the second postoperative day and post-mortem was refused.

#### METHODS OF TREATMENT

A ventriculogram was done in 5 of my cases with no untoward results and with invaluable aid as to correct localization of the clot. An encephalogram was unsatisfactory in the sixth case. Furthermore, the simple procedure of ventriculography introduces little hazard in the patient with intracerebral bleeding. Neurologic examination, be it ever so complete and suggestive, is not sufficient.

Two operative procedures have been used in the patients reported by the various authors. These are: a burr hole, with needling of the suspected area and evacuation of the old blood or clot; and an osteoplastic flap raised, with complete exploration of the diseased area demonstrated by ventriculogram.

The latter procedure is the one which I endorse and advocate. I do so for the following reasons: adequate exposure, complete control of bleeding, and removal of all macerated brain tissue. The wound is then closed without drainage.

#### COMMENT

In comparative analysis of the symptoms of my 6 cases, I find considerable similarity to those which have been abstracted from the literature. The predominant features to be remembered are headaches, dimness of vision or other visual symptoms associated with hemiplegia, and papilledema. When this group of findings is present, subcortical bleeding with clot formation must be considered in the differential diagnosis. It is interesting to note that, of the 23 cases analyzed, a diagnosis of brain tumor was made in 12 instances. Hemorrhage with clot formation was diagnosed in 4 and no preoperative diagnosis was given in the remaining 7 cases.

#### SUMMARY AND CONCLUSIONS

1. Six cases of spontaneous subcortical bleeding with clot formation are reported with operative intervention.
2. Accurate localization of the lesion by ventriculography is a necessity in these patients.
3. Complete exposure of the diseased area by an osteoplastic flap for the removal of clot, macerated tissue, and control of bleeding is very essential.
4. Aspiration of the clot through perforator openings is to be discouraged.

5. While it is difficult to make a diagnosis in these patients, the chief difficulty seems to be that the diagnosis is not usually considered.

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## THE DIAGNOSIS AND TREATMENT OF SUBDURAL HEMATOMAS

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### INTRODUCTION

**I**NTRACRANIAL hemorrhage due to trauma is as old as trauma itself. As soon as our ancestors began to fall out of trees and to hit each other on the head with stones or clubs they undoubtedly began to have traumatic intracranial hemorrhages. This paper deals with traumatic subdural hemorrhage; that is, the accumulation of blood in the subdural space; and it includes a series of thirty-five consecutive cases operated on by me.

Subdural hematoma was familiar to the pathologist long before the surgeon began to treat it. Johannes Wepfer (1657) has been given credit for the first authentic description of this condition. D'Enrico and German quote him as finding at necropsy a large blood-filled cyst beneath the dura of a patient who had died after an "apoplectic stroke." Virchow's paper in 1857 on the subject was accepted as the final word for many years and consequently generations of pathologists and many surgeons as well considered subdural hematomas to be spontaneous in origin and designated them as pachymeningitis hemorrhagica interna. In 1914 Trotter took issue with this view and in an article which can hardly be improved upon twenty-six years later stated that the condition was post-traumatic and that the source of the hemorrhage was rupture of one of the superior cerebral veins as it traversed the subarachnoid and subdural spaces to enter a dural lacuna. He reported four cases with two deaths. The two deaths were in cases with bilateral hematomas and in both cases the brain failed to expand after evacuation of the clots, a complication that is still exceedingly troublesome to the surgeon. However, this single article could not offset the tremendous weight of Virchow's opinion and the subject of subdural hematoma was still closed until Putnam and Cushing published their study in 1925. They attempted to differentiate between the reactive or traumatic and the spontaneous hematomas, but they were forced to admit that the histologic differences seen in the membranes of the two types were only slight. In this paper only the traumatic subdural hematomas are considered as they are the ones that primarily interest the surgeon. The spontaneous ones are usually associated with systemic disease, blood dyscrasias, or carcinomatosis or sarcomatosis of the dura (Russell and Cairns) and seldom come to the attention of the surgeon. It is only

necessary to add that the origin of traumatic subdural bleeding may be not only from rupture of superior cerebral veins (Trotter), but also from inferior cerebral veins which enter the sphenoparietal sinus, veins which enter the lateral sinus from the posterior or inferior surface of the temporal lobe, and at times, even from anomalous cerebral veins that may enter the dura from the convexity of the hemisphere.

#### CLASSIFICATION

The classification of subdural accumulations of blood or fluid has been troublesome and there is little agreement. These accumulations range from fresh fluid or soft blood clots to encapsulated collections of bile-colored fluid and even to accumulations (nonencapsulated) of xanthochromic fluid in the subdural space (subdural hydroma). Cases of the latter are not included in this report.

Leary classified subdural hematomas under five heads: (1) fresh fluid or soft clots, (2) firm clots, (3) chocolate-colored fluid with a neomembrane on the dural side, (4) chocolate-colored fluid enclosed in a double membrane, and (5) a fused double subdural neomembrane with absorption of the previously enclosed clot. These various stages do occur, but, for practical surgical purposes, the classification into acute and chronic types suffices. Some surgeons have questioned the rationale of dividing the traumatic subdural hematomas into acute and chronic groups since it is now generally recognized that they are all varying stages of the same lesion. I believe that there is ample clinical justification for this. The acute subdural clots are usually associated with brain injury, are relatively large to begin with, follow severe head trauma, and have a correspondingly high mortality. From a diagnostic standpoint they are to be differentiated from cases of localized brain injury and extradural hematoma. The chronic subdural hematomas usually are not associated with severe brain injury, or the patient has recovered from his brain injury; the clots are primarily small; they often follow slight trauma; and, if the condition is recognized before increased intracranial pressure has placed the patient in too precarious a state, the mortality is low. They have to be differentiated from slowly expanding lesions; e.g., tumor or abscess.

Chronic subdural hematoma has received by far the most attention in the literature. Out of fifty-five articles reviewed in the course of preparation of this paper, only six mention acute subdural hematoma. In the neurosurgical clinics the greatest experience has been with chronic subdural hematoma. Only in large emergency services has there been much experience with the acute types.

Great interest has been attached to the formation of the chronic subdural hematoma. It must be emphasized that these clots, even when solid or semisolid, show no lamellation or other evidence of repeated hemorrhages. It is probable that in only rare cases does repeated hemor-

rhage occur from either the original torn vessel or from the vessels of the capsule or neomembrane. The early clots are never encapsulated, which speaks against a possible intradural origin, as does the fact that, in successive stages of the formation of a neomembrane, it is always formed first on the dural side and that in old cases only does the neomembrane on the arachnoid side equal in development that on the dural side.

There is considerable variation in individual cases in the rapidity with which a neomembrane is formed. On the one extreme I have seen fairly well developed neomembranes within seven days after the injury that presumably caused the original hemorrhage; on the other extreme I have seen little evidence of neomembranes and semisolid clots as long as six weeks after the injury. In both cases the history appeared dependable.

Gardner, Zollinger and Gross, and Munro have developed the modern theory of the development of the large chronic subdural hematoma from a relatively small initial clot in the subdural space by the absorption of cerebrospinal fluid into the clot by osmosis. At first there is an equalization of osmotic pressure with the whole blood of the clot. As hemolysis of the whole blood takes place, the process is tremendously accelerated by the resultant great increase in osmotic pressure following the breakdown of large protein molecules.

#### DIAGNOSIS

The two sexes seem equally disposed to the development of these clots, although the greater frequency of head injury in the male makes them more frequent in that sex. In my series there were 26 in males and 9 in females. They were distributed between the ages of 20 and 70 years, although most of the cases occurred in the fifth decade. Age is an important factor in survival; there were only 3 survivals in the 10 cases occurring in the sixth and seventh decades of life (Table I).

The recognition of the acute subdural hematoma to a considerable extent parallels that of the extradural hematoma. Preoperatively it is often difficult, if not impossible, to differentiate the two, although typically the extradural clot gives an earlier onset of symptoms because it is usually due to arterial bleeding. The recognition of both depends essentially on the progression of symptoms. Of all the symptoms that may be produced by a developing hematoma, alteration of the state of consciousness is the most significant. Often restlessness and delirium in previously quiet and rational patients are the first signs of a developing hematoma. When initial injury to the brain has been slight there will be the classic "lucid interval" between the injury and the time the clot develops sufficiently to cause stupor or coma. In most cases of acute subdural hematoma there is severe initial injury to the brain and consciousness is never regained. Only the deepening of stupor or coma indicates the development of the hematoma.

Dilation of the homolateral pupil is one of the most dependable localizing signs of a hematoma in my experience, and, in addition, is a valuable sign of a developing clot when it appears after the patient has come under observation. If present at the time of admission to the hospital, it usually means localized brain injury. Thirteen patients in the series had a unilateral dilation of the pupil and in 12 dilation was homolateral to the clot. Of these 13 cases, nine were chronic and four were acute hematomas. The 1 case in which the dilation of the pupil was contralateral to the clot was in an acute hematoma. The exploration was unilateral and there may have been brain injury or another hematoma on the side of the dilated pupil. The patient lived two weeks. Death was thought to be due to pulmonary complications. Unfortunately necropsy was not performed.

Convulsions, if Jacksonian, are of great localizing value and usually indicate a hematoma, either extra- or subdural, although they may result from localized cerebral contusion or edema. They were present in 4 cases. Weakness or paralysis of the extremities with abnormal or pathologic reflexes is usually contralateral to the lesion; occasionally with a large hematoma, the contralateral crus cerebri is pressed against the free edge of the incisura tentorii and hemiparesis and pyramidal tract signs are produced homolateral to the clot. The presence of hemiparesis or signs of unilateral involvement of the pyramidal tracts, especially if progressive, is strong presumptive evidence of a hematoma, but it, too, may be produced by localized brain injury. This finding was present in 19 of the 35 cases; it was contralateral to the clot in 13, homolateral in 6. The combination of homolateral dilation of the pupil and homolateral hemiparesis was seen in 2 patients; 1 had an acute hematoma, the other, a chronic. Localizing neurologic signs of some type were present in 24 of the 35 patients.

A slow pulse rate indicates the compensatory action of the cardiovascular center in response to increased intracranial pressure. Typically, the blood pressure will rise with the fall in pulse rate and an abnormally high pulse pressure will be present. It is helpful to record graphically the systolic and diastolic pressures and the pulse rate on the same chart. When compensation begins to fail, the pulse rate will rise and the systolic pressure will fall. When these two lines cross, the condition of the patient is usually precarious and the peripheral circulation is inadequate. The systolic pressure always falls more rapidly than the diastolic and the pulse pressure consequently rapidly becomes progressively lower. A high body temperature is another dependable sign of dangerously high intracranial pressure, as is an irregular respiratory rate, although this latter is so variable that it is difficult to make definite statements about it.

It is evident that any or all of the phenomena discussed in the foregoing paragraphs may be caused by localized cerebral injury (lacera-

tions, contusions, or even edema) and consequently are not diagnostic of a hematoma. However, it is rare to meet with an acute hematoma, epidural or subdural, that does not give one or more of these symptoms.

Symptoms of a chronic subdural hematoma do not appear for days or weeks, some times even months, after the original injury which may be forgotten either because of its apparent insignificance or because the patient has so completely recovered from its effects. The clinical picture is usually progressive. Mental disturbances often predominate and many of these patients are considered to be suffering from a psychosis. Headache and vomiting are often present and objective evidence of increased intracranial pressure in the shape of papilledema is often present. Record of a fundus examination was made in all but 2 cases of the series. Papilledema was present in 14 patients. All had chronic hematomas.

The spinal fluid was examined in 26 patients. Five of these had acute subdural hematomas; in all of them the fluid was blood tinged. In the 21 patients with chronic hematomas in which the fluid was examined, it was xanthochromic in 16. No examination of the spinal fluid was made in 4 patients with acute and 5 with chronic hematomas.

Air studies were made in only 1 patient in the series. This man had a choked disk, gave no history of injury, and had no localizing signs. Ventriculography revealed evidence of a space-occupying lesion in the right frontal lobe. Craniotomy exposed a small chronic subdural hematoma over the right frontal lobe. The openings in the parieto-occipital regions for ventriculography had failed to reveal the small hematoma. The patient later recalled several minor head traumas in the preceding six months.

#### TREATMENT

The methods employed by surgeons in dealing with these cases have ranged from large osteoplastic flaps to simple drainage through burr holes as originally and independently advised by Fleming and Jones and McKenzie in 1932. In only two cases in the present series has an osteoplastic flap been reflected. One has already been referred to; the case in which ventriculography was performed. In the other, because of the failure of the patient to rally after drainage of a large, well-encapsulated clot, an osteoplastic flap was reflected nine days later and the entire capsule meticulously removed. In spite of this, death occurred two days after this procedure. I feel this failure was due not to retention of the membranes of the clot after simple burr-hole drainage, but rather to failure of the brain to expand to occupy the space previously occupied by the clot. This point will be discussed further a little later.

Our practice when a subdural hematoma is suspected is to make a small (4 cm.) vertical scalp incision in the midparietal region above the ear, and after retraction of the scalp with a small self-retaining retractor, to make a burr hole just above the insertion of the temporal muscle. This can be done under local anesthesia in the great majority of cases.

If the patient is too restless or uncooperative for this, avertin may be used as a preliminary basal anesthetic.

If a subdural clot is present, this burr hole will reveal it in the great majority of cases. Since these clots are in the subdural space, of necessity they assume a pancakelike shape, spreading out over the surface of the hemisphere but being thickest at their point of origin. As we have pointed out, there are usually four possibilities for this origin. If the original bleeding has been from a superior cerebral vein, the clot's greatest mass will be toward the midline; if from an inferior cerebral vein entering the sphenoparietal sinns, the clot will be largely anterior and inferior. Clots arising from hemorrhage from veins passing from the posterior part of the temporal or occipital lobes to the lateral sinus will be predominantly posterior and inferior in location. Finally, those arising from tears in anomalous veins between the convexity of the hemisphere and the dura will have their greatest thickness over the convexity of the hemisphere.

If the case is an early one and an extradural hematoma is by chance present, this burr hole will likewise disclose it. The appearance of the dura can be depended on to reveal whether there is a subdural hematoma, as even fresh blood beneath the dura can be recognized by the abnormal darkening which it produces. It is my custom to enlarge the burr hole with rongeurs to a diameter of approximately 3 cm. before opening the dura if it is discolored. This opening is not in any sense a decompression, but does give room for such manipulations as are usually necessary.

After the dura is opened, the clot can be readily evacuated in the great majority of cases. If the clot is solid or semisolid, simple alternate irrigation with saline solution and suction through a catheter passed beneath the dura will serve to break it up. Irrigation with saline solution must be done cautiously or not at all in acute cases because of the swelling of the brain which it induces and which is often already present. In chronic cases there is often difficulty in getting the brain to expand and here repeated irrigations may be of value.

Occasionally, the primary burr hole may be near the edge of the clot; in such cases it is a simple matter to place another one over the center of the now localized clot. If the original burr hole does not reveal the clot and there is sufficient evidence, additional burr holes may be placed anteriorly and posteriorly. In all cases where a clot is not revealed on the suspected side, an exploration must be made on the opposite side. Failure to do this resulted in overlooking the clot in one patient in the series. Necropsy two days later revealed the clot on the opposite side. Attention has already been called to the frequency of false localizing signs in these cases. In this series homolateral hemiparesis or pyramidal tract signs were present in over 30 per cent of the cases that showed



such symptoms. Extracerebral space-occupying lesions would seem more likely to press the contralateral crus cerebri against the free edge of the tentorium.

Even when a clot is disclosed on the side first explored, it is wise in most cases to put a burr hole on the opposite side. Four patients in the present series had bilateral clots. In three cases both clots were discovered and evacuated at the original operation; all three patients recovered. In the fourth case the two explorations were a week apart. The second was undertaken because of the lack of satisfactory improvement after removal of the first clot. Death occurred from meningitis four days after the second operation.

In older individuals and especially in cases that come to the surgeon late, one occasionally finds that the cerebral hemisphere does not expand to fill the space formerly occupied by the clot. Trotter noted this in the two fatalities that he reported. Both Grant and Coleman in 1935 called attention to the grave prognostic value of this observation. Cohen reported a remarkable case of this type with final recovery after repeated aspirations of the subdural space. In my experience these cases all terminated fatally, in spite of drainage of the subdural space and post-operative intravenous administration of isotonic fluids in an attempt to swell the brain. Finally, at the suggestion of Dr. Jerry Kearns, I initiated a special technique for dealing with them. Now when at the operating table a brain fails to expand to occupy the space previously occupied by the clot after the clot has been thoroughly evacuated, the subdural space is filled with distilled water. A small tube drain is placed beneath the dura and the wound then closed in layers tightly about the tube. A clamp is placed on the tube, the head dressed, and the patient returned to bed. He is given 1,000 c.c. of distilled water intravenously followed by 1,000 c.c. of normal saline solution. The clamp is removed from the tube four to six hours later. This method was used in five such cases in the present series with four recoveries. In the patient that failed to recover, the technique was modified by the omission of the intravenous administration of distilled water; only normal saline solution was given intravenously. This patient followed the usual course of such cases in my past experience; he failed to rally, remained in coma, and died forty-eight hours later.

The danger of hemolysis following the intravenous administration of distilled water is obvious; in the four cases in which it was used, mild hemoglobinuria was noted for a day or two following the injection. However, no ill effects were noted clinically in any of the four cases. Its use is justified by the comparison of the previous poor result constantly encountered in this type of case with the success that this technique has met with.

In the case of either subdural clot or negative exploration, I like to place a drain of rubber tissue beneath the dura for twenty-four hours. It should not be left in place any longer but removed at the initial dressing the next day. This drain will take care of the slight oozing that may otherwise take place after the wound has been closed. More important is the provision for continuous supratentorial drainage of cerebrospinal fluid for the first twenty-four hours. This in itself may be of great help to the patient and has none of the dangers of lumbar drainage. The risk of infection is minimal and to my mind is offset by the advantages of drainage. These wounds are always closed in layers with interrupted silk sutures in the temporal muscles, fascia, galea, and skin.

#### SUMMARY OF CASES

The series of subdural hematomas reported here consists of 35 consecutive cases operated upon with a mortality of 43 per cent for the entire group. The mortality was 24 per cent for cases operated upon more than three days after the injury. Clots were removed in 34 cases. In 1 case, already referred to, the clot was not found on the side indicated by the neurologic findings and unfortunately the other side was not explored.

Nine of the 15 deaths were in cases operated upon within three days after the injury. Necropsy was performed by the coroner's physician in 5 of these cases; cerebral contusion or laceration was present in all. One of these cases has already been referred to; the patient with bilateral subdural clots who had two explorations a week apart and who succumbed to meningitis after the second exploration. Necropsy was performed in 5 of the 6 deaths occurring in cases operated upon more than three days after the injury. One of the patients, as already stated, had an unrecognized clot on the side opposite to that explored. The other 4 had pulmonary pathology of bronchopneumonia or lung abscess which was thought to be the immediate cause of death.

The cases are classified according to time elapsed between the injury and the date of operation in Table II. Here, of course, history at times may be unreliable. In Table III the hematomas are classified according to apparent age as judged by the appearance of the clot, the presence or absence of associated cerebral injury as disclosed at operation or

TABLE I

DECADE OF LIFE	LIVING	DEAD	TOTAL
3rd	4	1	5
4th	5	3	8
5th	8	4	12
6th	2	3	5
7th	1	4	5
Total	20	15	35

necropsy, and the size of the clot. In this table "acute type of clot" refers to solid, liquid, or semisolid fresh clots with no evidence of formation of neomembranes, even on the dural side.

It is evident from these tables that the mortality is very high in the acute or early subdural hematoma; that is, in unencapsulated clots operated upon within three days of the injury. These clots are often associated with cerebral injury, which is, I feel, the most important factor in

TABLE II

TIME BETWEEN INJURY AND OPERATION	LIVING	DEAD	TOTAL
1 to 3 days	1	9	10
4 to 14 days	8	2	10
Over 14 days	11	4	15
Total	20	15	35

the high mortality. Size of the clot is not so important, as the greatest mortality occurred in moderately sized clots. This group included most of the acute clots. As a result of my experience I have ceased operating upon the acute or early subdural hematoma except in those cases which are accidentally disclosed in the course of an exploration for an epidural hematoma.

TABLE III

	LIVING	DEAD	TOTAL
Acute type of clot	1	8	9
Chronic type of clot	19	7	26
Associated cerebral injury present	2	6	8
Associated cerebral injury absent	18	9	27
Clot up to 1 cm. in thickness	8	2	10
Clot 1 to 2 cm. in thickness	7	9	16
Clot over 2 cm. in thickness	5	4	9

## CONCLUSIONS

In conclusion I would emphasize that acute, subacute, and chronic subdural hematomas are all progressive stages of the same lesion. Nevertheless, clinical differentiation can and should be made between the acute, or early, and chronic, or late, subdural hematoma. This differentiation is based on the early large size of the acute clots, their association with more or less extensive cerebral injury, and the high operative mortality.

The mortality is high in acute or early clots, in cases of associated cerebral injury, and in old people. Chronic or late subdural hematomas in young or middle-aged people without associated systemic disease have a good prognosis if operated upon before the effects of increased intracranial pressure have rendered the patient moribund.

Drainage through burr holes is satisfactory in the great majority of cases and subtemporal decompression or an osteoplastic flap is rarely necessary. In no case of death in this series was recurrence of the clot found at necropsy.

Bilateral exploration should always be done, especially if no clot is found on the side first explored. As already indicated, two deaths in this series are due to failure to observe this.

If, at the operating table, the brain does not expand to fill the space previously occupied by the clot that has been evacuated, special measures to induce expansion of the brain must be instituted. My particular procedure has been described.

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## RECONSTRUCTIVE OTOPLASTY

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COMPLETE or partial reconstruction of the external ear has long been one of the major problems in plastic surgery. The chief stumbling block in rebuilding a new ear lies with the problem of furnishing an adequate support to the overlying skin. The numerous curves and levels of the normal ear cartilage make replacement of this tissue an important undertaking.

Prior to the following procedure the best attempt toward supplying a supporting framework consisted in the utilization of costal cartilage or a bone graft from the iliac crest that was shaped to represent the missing ear cartilage. Obviously neither source gave adequate material from which one could carve a structure that would closely represent the normal auricle, regardless of how adept the operator was as a sculptor. The most one could accomplish was to give the patient a poorly shaped rim or helix. The net result of such operative procedures was always disappointing, both to the operator and patient. Pierce,<sup>1</sup> Padgett,<sup>2</sup> and Kirkham<sup>3</sup> have revived the utilization of carved costal cartilage and, while their results are superior to those of their predecessors, several finer points are still lacking.

The use of any foreign material, whether it be metal, ivory, celluloid, or the like, is only to be mentioned because of the failures that result. Such material is not tolerated and like all foreign bodies is sooner or later extruded.

Before discussing plastic reconstruction it should be recalled that there appear to be only two tissues that can be successfully transplanted from one individual to another, namely cornea and cartilage. The success of transplant of these two tissues apparently is dependent upon the fact that neither has a blood supply and that they are kept alive by absorbing nutriment from adjacent soft tissues.

With the above in mind, we have been following the method recently devised by Gillies,<sup>4</sup> where an ear cartilage taken from another individual is used. The donor has always been and should always be a woman, who can cover the donor ear with her hair.

Since external ear defects commonly occur in children, the patient's mother is usually chosen as the cartilage donor. There is no special reason for choosing the mother except that she is invariably willing to do this for her child and thus the availability of an ear cartilage becomes more simplified.

After preliminary surgical preparation, an impression of the donor's ear is first cast with warm, sterile dental modeling compound (Fig. 1). When hard it is removed and temporarily laid to one side.

To remove the cartilage, an incision is made along the posterior rim of the helix, exposing either all of the cartilage or whatever part is needed. The skin is then dissected from the anterior and posterior aspects of the cartilage, during which time careful attention is paid not to fracture the cartilage or perforate the skin during the process. After being completely freed, it can now be removed easily. The incision in the donor's ear is then sutured. The previously prepared mold (Fig 1)

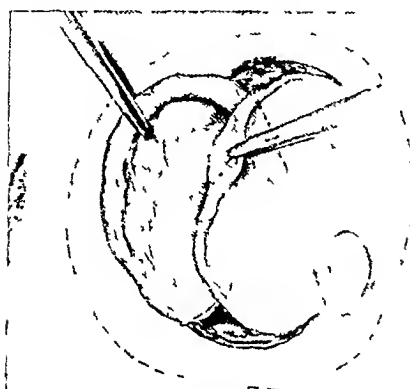
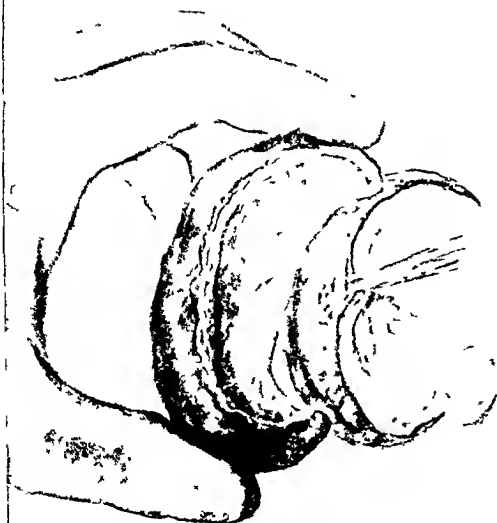


Fig 1 Mold cast of donor ear prior to removal of cartilage  
Fig 3 Ear cartilage being transferred to prepared subcutaneous pocket in temporal mastoid region  
Fig 4 Cartilage has been elevated away from temporal mastoid area Stent graft being inserted to cover posterior cartilage defect and temporal area

3.



4.



1

is again placed upon the anterior aspect of the ear and secured by bandaging under moderate pressure. This procedure insures accurate coaptation of the two skin flaps. Although one may expect to have the completely unsupported ear tend to droop or shrivel, it is surprising how rigid they sometimes become due to the formation of a firm scar between the anterior and posterior skin coverings (Fig. 2). However, should any deformity occur, the donor can easily disguise this with her hair. The sacrifice is not, however, nearly as mutilating as one might suspect.



FIG. 2.—Donor ear showing healed state after removal of cartilage.

A curved incision corresponding to the normal anatomical location of the helix is now made through the hairless skin overlying the temporal and mastoid areas of the recipient. The skin is mobilized by freely undermining in all directions. After completing hemostasis the ear cartilage is then passed through this incision and placed in a normal anatomical position, following which the skin wound is closed (Fig. 3). Pressure is then made over the newly placed cartilage with a moist sterile marine sponge, held in place by bandaging. Small bits of the sponge may be cut out to fill in accurately all the underlying depressions to insure adequate adherence to each of the various ridges and concavities.

In three to ten weeks it will be noted that the mastoid skin is firmly adherent to the anterior aspect of the newly transplanted cartilage. At this time the original incision may be reopened around the rim of the cartilage, leaving a broad pedicle attached anteriorly. The entire mass is then lifted forward until it stands as a normal ear, matching its fellow on the opposite side. There now exists what appears to be a normal

ear from in front, but with a skin defect overlying the mastoid process and on the posterior aspect of the cartilage. This area is now covered by a Stent graft.

A piece of sterile warm pliable dental modeling compound is next pressed into shape to fit the defect behind the ear and mastoid process. After this has been permitted to harden, it is removed and covered with one single thick split-skin graft; that is, one large enough to cover both the mastoid and posterior cartilage defects. This graft is then spread over the mold with the raw surface outward, following which it



Fig. 5.



Fig 6

Figs. 5 and 6.—Results of illustrated case. Existing primary skin tab has been rotated downward to become new lobule.

is reinserted into the defect behind the ear (Fig. 4) and is secured in place by a pressure bandage. Approximately one week later the bandage is reopened, the Stent mold removed, and the excess graft trimmed away. An ear of normal appearance is now observed, the transplanted cartilage being lined on the anterior aspect by the former mastoid skin and on the posterior side and mastoid process by newly grafted skin (Fig. 6).

For reconstructing partial losses, obvious modifications of the steps described may be carried out.

In congenital defects there is frequently a small tab of skin that can be swung downward to become the new ear lobule. If this is absent, a small tube pedicle flap raised nearby will furnish sufficient skin for this purpose.



The question has been raised as to what is the better time in which to reconstruct these congenital defects. As with other congenital disorders the results on the whole are usually best when done at the earliest age that the child will stand operation and cooperate. While the surgical problem is easier during the teens, from the psychological standpoint it is wiser to have this defect repaired before the child becomes too conscious of his abnormality; that is, before school age. We are not certain to date whether this ear will grow at the same rate as the normal ear, but it apparently remains at approximately the same size so that, even though the ear may be slightly larger at first, it will eventually match the one on the other side.

The average layman (and doctor) always asks about the question of reconstruction of the external auditory canal when this is absent due to congenital anomaly. We very definitely feel that this should not be attempted unless coincidental deafness exists. This operation is difficult to perform and is apt to be unsuccessful even though the canal has been re-established, because of the problem of maintaining its patency. From the practical standpoint these children seem to hear as well from use of their normal ear, thus making this surgery unnecessary. In other words, we are dealing chiefly with a cosmetic problem; the functional aspect is ordinarily but of secondary importance.

In conclusion, the following thought should be remembered. Many physicians see individuals who have just lost all or part of an ear in an accident. If the lost portion is completely detached, suturing it in place holds very little promise of success even if done immediately after the accident. On the other hand, this portion should never be discarded, but the cartilage should be saved for future reconstruction. If it is not feasible to bury it under the mastoid skin at once, it may be sutured into a subcutaneous pocket in the abdominal wall until one is prepared to place it in its permanent location.

#### SUMMARY

An operative procedure as recently developed by Gillies for the permanent replacement of the external ear has been described and found to be uniformly superior to previous methods. The operation utilizes an ear cartilage taken from another individual as the basis of the reconstruction. Such an architectural form gives far better cosmetic results than former operative procedures.

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# CHRONIC UNDERMINING BURROWING ULCER

REPORT OF CASE TREATED BY LOCAL APPLICATIONS OF SULFANILAMIDE

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CHRONIC progressive ulcers present a definite clinical entity and respond poorly to the usual therapeutic procedures. Meleney<sup>1, 2</sup> has described two types, one a "symbiotic progressive gangrenous ulcer," with gangrene of the skin margin but without undermining or deep penetration. This type is caused by the symbiotic action of a microaerophilic nonhemolytic streptococcus and a *Staphylococcus aureus*. These ulcers usually follow drainage of an intra-abdominal abscess or thoracotomy. The involved skin presents three characteristic zones: the outer, a bright red; the middle, a dusky purple; and an inner, gangrenous. The second type Meleney refers to as "chronic undermining nongangrenous burrowing ulcer." Here the infection burrows into the deep tissues, but there is no gangrene of the skin. The ulcers originate around chronic sinuses, produce liquefaction of the subcutaneous fat and connective tissues, and result in undermining of the skin margins. Recently Meleney<sup>3</sup> stated: "Chronic undermining ulcer is not a symbiotic infection but caused simply and solely by the microaerophilic hemolytic streptococcus."

Other authors refer to chronic progressive ulcers under the general term of "phagedenic ulcers."<sup>4, 5</sup> Most investigators have confirmed Meleney's work concerning the presence of anaerobic streptococci.<sup>6, 7</sup> As one reviews the cases reported, the majority of them fall into one of these two clinical entities. Meleney has recently classified chronic undermining burrowing ulcers into three types: the postoperative, the lymph glandular, and the secondarily contaminated. On the basis of this classification the following case belongs to the lymph glandular type.

## CASE REPORT

F. J., a 32-year-old white male, was first admitted to the University Hospitals on March 13, 1939. One year prior to admission he developed an infection on the dorsum of his right hand, followed by an axillary suppurative adenitis which was drained on seven occasions and resulted in multiple draining sinuses. On routine physical examination the systems were found to be essentially normal. There was marked induration of the axilla extending halfway between the anterior axillary fold and the sternum and down on the chest wall as far as the fourth rib. Serologic tests for syphilis and agglutination studies for undulant fever, typhoid, and tularemia were all negative. Cultures from the sinuses grew the microaerophilic beta-hemolytic streptococcus and some diphtheroids. Repeated bacteriologic and pathologic examinations were made for fungi and tuberculosis, but none were found. A wide excision of the sinus tracts was performed on the first admission. The wound was treated with alternating dressings saturated with Dakin's solution and normal saline solution. At the time of discharge, May 3, 1939, a granulating surface 8 cm.

in diameter was present. The edges were epithelializing and it was thought that the wound would heal.

The patient was readmitted to the hospital on June 26, 1939. During his stay at home daily dry dressings were applied. The ulcer had increased in size, measuring 13 cm. in diameter. Its base was covered with dirty gray granulation tissue and the edges had become undermined. An aerobic beta-hemolytic streptococcus and a *Staphylococcus aureus* were isolated. No anaerobic cultures were made. Three days after entering the hospital the undermined skin edges were excised. During the following eleven weeks numerous methods were used in an attempt to obtain a clean granulating surface. Dakin's solution, potassium permanganate, zephiran, and azo-chloramide were all tried. Sulfanilamide was given orally for eight days in doses which maintained a blood sulfanilamide level of 6 to 10 mg. per cent. Some improvement was obtained and grafting was subsequently attempted on two occasions without success. He left the hospital Sept. 14, 1939, because of a death in his family, without any appreciable change in the wound.

His third admission was on Jan. 29, 1940. The ulcer had further increased in size, measuring 20 cm. in diameter. Undermining of the edges was marked. No strictly anaerobic organisms were found, but an aerobic beta-hemolytic streptococcus was found and we now believe that more diligent studies would have revealed that this organism was the microaerophilic beta-hemolytic streptococcus which was isolated on the first admission. A *Staphylococcus aureus* was also isolated. The patient had developed a secondary anemia and for this he was transfused and given general supportive treatment. Zinc peroxide\* applied locally for one week was followed by beginning epithelialization at the wound edges, but there remained a large amount of purulent exudate. Skin grafting was again unsuccessful except for two small grafts which remained viable. Realizing that a beta-hemolytic streptococcus was the predominant organism, and hoping for some treatment that would improve the condition of the wound more rapidly, local applications of sulfanilamide were instituted. The wound was covered with powdered sulfanilamide, and a gauze dressing, moistened with distilled water, was applied. Crusts of dried exudate were removed daily and sulfanilamide applied. After three days the granulations were bright red and the exudate had decreased about 90 per cent. Epithelium started to grow in from the wound edges and the two grafts which had survived rapidly increased in size. Grafting was repeated using small Thiersch grafts. These were left dry for six hours and then a moist dressing of sulfanilamide solution was applied. The solution was freshly prepared by dissolving 10 Gm. of powdered sulfanilamide in 1 liter of near-boiling water. Eleven days after the final skin grafting the wound was completely epithelialized. A recent follow-up revealed that the patient has remained well.

When these progressive ulcers were first recognized, wide excision was advocated. This is often satisfactory in the cases classified as "symbiotic progressive gangrenous ulcer." However, in the group of "chronic undermining burrowing non-gangrenous ulcer," excision alone is not adequate. Holman<sup>4</sup> treated a small series with maggots. Innumerable antiseptic preparations have been tried without success. Meleney and Harvey<sup>5</sup> have stressed the fact that all preparations of zinc peroxide are not active and have shown that certain technical features of the application must be strictly followed. Other authors<sup>6, 7</sup> have confirmed the value of zinc peroxide.

\*Merck's zinc peroxide was tested for use and found to be "active." The test was carried out by adding distilled water to the preparation. The supernatant fluid became clear and contained bubbles.

Sulfanilamide has been given orally in many types of wounds. Goodman<sup>8</sup> reported improvement in chronic ulcers on extremities culturing aerobic streptococci. Meleney and Harvey<sup>3</sup> used sulfanilamide alone and in conjunction with zinc peroxide. They concluded: "It is possible for sulfanilamide [oral] to result in the healing of certain of these ulcers without the local use of zinc peroxide. However, the process of healing was very much longer than in the cases treated with zinc peroxide alone or with a combination of the two forms of treatment."

Several authors have reported successful local use of sulfanilamide. Jensen and Johnsrud<sup>9</sup> found it effective in preventing infection of compound fractures. It has been found to be of value in treating chancreoid.<sup>10</sup> Long<sup>11</sup> used the drug in treating chronically infected superficial lesions from which beta-hemolytic streptococci were isolated. Sinclair<sup>12</sup> applied the drug to infected tooth sockets.

It is not the purpose of this paper to refute the value of zinc peroxide in the treatment of chronic undermining burrowing ulcers, since many cases of this type have been successfully treated by this method. However, it is our desire to present a case in which the local application of sulfanilamide brought about a more rapid improvement than was obtained with zinc peroxide and subsequently enabled successful grafting.

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## ABSCESS OF THE LUNG

### BRONCHOPULMONARY SEGMENT, BASIS FOR CLINICAL LOCALIZATION

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IN A previous paper<sup>1</sup> attention was called to the observation that lung abscess developed in and was confined to, in the early stages, anatomical pulmonary units which were named bronchopulmonary segments. It was also shown that these segments were essentially constant in form and position and, because of their relationship to bronchi, could be designated in bronchoscopic localization. In a later paper<sup>2</sup> the significance of bronchopulmonary segments in roentgenologic interpretation was indicated. The anatomical studies which were made of the bronchi of these segments were in complete agreement with the classical studies of Ewart.<sup>3</sup> The term bronchopulmonary segment was devised, not to suggest a new anatomical relationship, but to place emphasis on a clinical pathologic view. The necessity for such emphasis became apparent as evidence accumulated that localized pathologic processes, such as putrid lung abscesses, bronchiectasis, and gangrenous bronchopneumonia, evolved in bronchopulmonary segments.

In the surgical treatment of pulmonary abscess, accurate localization is of primary importance if the best results are to be obtained by drainage operations. With precise localization the operative procedure<sup>4</sup> is usually simple, consisting of a limited exposure at the site of contact of the abscess with the thoracic parietes and incision, through adhesions, of the abscess. The free pleural space and normal pulmonary tissue are not traversed in such a precise one-stage operation, and severe, and frequently fatal, putrid empyema is avoided and excellent results can be achieved. Without the knowledge of the exact site of the lesion, the free pleural space and the normal lung may be seriously infected at operation.

The purpose of this paper is to present the anatomical basis for the localization of lung abscess and the general approach to the problem used at Mt. Sinai Hospital. In this institution on the surgical service 104 cases<sup>5</sup> of acute putrid lung abscess have been operated upon with four deaths. Apart from questions of surgical technique, the excellent results which have been obtained and the low mortality are in large part ascribable to accurate localization.

Before describing in detail the basic principles of localization, a résumé will be given of certain constant anatomical characteristics of lung abscesses as observed over a period of about ten years in a series

of over 350 acute, subacute, and chronic cases. Emphasis should be placed on the fact that the statements to be made apply only to putrid pulmonary abscesses of substantial size and not to small cortical or miliary abscesses, small localized empyemas resembling pulmonary abscess, or nonputrid collections of pus from various sources.

1. Lung abscesses always lie in the periphery of the lobe, their most superficial portion being within one-quarter or one-half inch of the surface. The superficial situation is due to the onset of the disease in the finer bronchioles<sup>6</sup> which lie in the periphery. During the process of coalescence of necrotic foci into an abscess, the narrow layer of pulmonary tissue between the cavity and the pleural surface collapses and becomes a thin shell of infected tissue.

2. The superficial situation of pulmonary abscesses means easy surgical accessibility. There are exceptions in which abscesses, although quite as superficial as those facing costal surfaces, face interlobar fissures, the diaphragm, or the mediastinum.

3. The visceral and parietal pleurae over the abscess are practically always adherent and thus shut off the free pleural cavity. In only five cases in the entire series were costal adhesions absent and these were the instances referred to in the preceding paragraph.

4. There are sites of predilection. The lower lobe apical segment was the seat of the abscess in 40 per cent of the cases.

5. The lung abscess always lies in direct line with certain large bronchi. These bronchi are quite constant in number and position and the direction of the bronchi determines the direction of flow of the infected material and the position of the lesion. The reason for this relationship between the large bronchi and the abscess cavity is apparently that a spray or flood of infected material involving most of the fine bronchial branches is necessary to form a surgical lung abscess. Involvement of only one or two of these fine bronchi apparently produces very small cortical suppurative lesions which cannot be drained surgically. The breakdown of most of the branches of a larger bronchus produces the relationship noted between a cavity and a bronchus. This relationship of bronchus to cavity is important because, with a knowledge of the position of the bronchi shown to be practically constant, the sites of surgical abscess formation are known. In fact, long before the series of abscesses was studied, the possible locations of these lesions could be accurately predicted.

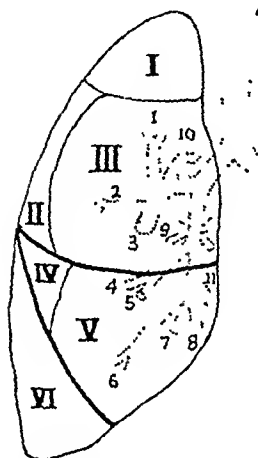
The bronchi which determine the position of the lung abscess are constant in number and position and are named according to the portion of lung into which they extend.

The pulmonary parenchyma supplied by each of the above-pictured bronchi may be outlined by injecting a colored fluid into the bronchus while the lung is moderately inflated. Fig. 1 shows these bronchi and segments and their nomenclature.

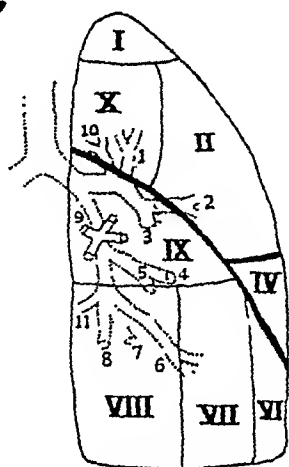
The anatomy of the bronchi and pulmonary segments described above has been corroborated by Neil and his co-workers.<sup>7</sup> Also of much interest is the fact that these workers have been able to demonstrate each bronchopulmonary segment *in vivo*<sup>8</sup> by injecting lipiodol through a catheter into a single segment and x-raying the subject.

## BRONCHOPULMONORY SEGMENTS WITH CORRESPONDING BRONCHI

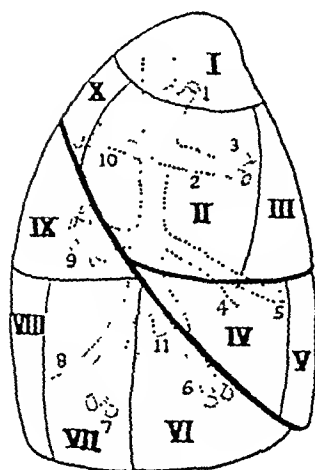
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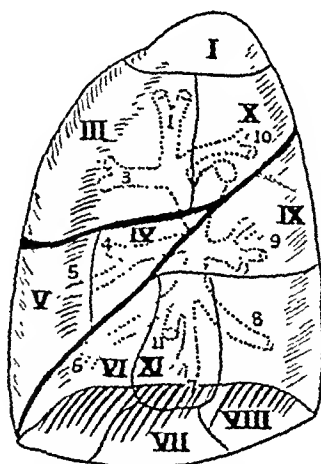
ANTERIOR VIEW



POSTERIOR VIEW



LATERAL VIEW



MESIAL VIEW

Fig. 1.—Arabic numerals identify bronchi and Roman numerals, their corresponding pulmonary segments in right lung. Left lung is the same except the mesial segment is rudimentary or absent. Upper lobe. Apical, 1; anterior, 3; axillary, 2; paravertebral (upper), 10. Middle lobe. Anterior, 5; axillary, 4. Lower lobe. Apical (middle paravertebral), 2; paravertebral (lower), 8; posterolateral, 7; anterolateral, 6; mesial, 11.

The bronchopulmonary segments are constant in position, shape, and number. Anatomically they are useful in describing and locating parts of the lung. Pathologically they are units of disease processes, such as lung abscess, gangrenous and suppurative bronchopneumonia, and bronchiectasis. Each segment has a definite position in the thoracic cage and a definite location on roentgen film. The main bronchus of each segment has a characteristic direction which determines the position of an abscess

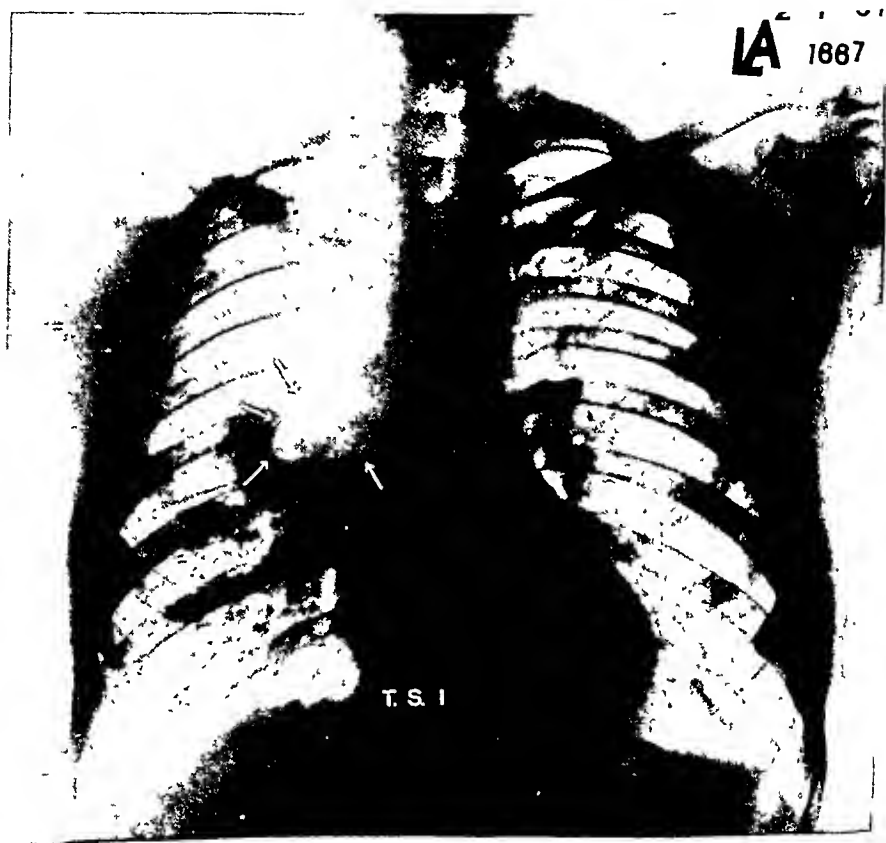


Fig. 2.—Posteroanterior plate showing lower lobe apical segment abscess (middle paravertebral abscess). This abscess must be drained posteriorly

in relation to the costal surface; that is, whether the abscess lies next to the paravertebral, axillary, or anterior costal surface. On the roentgen film the inner field shadows are all posterior abscesses, except mesial ones. The lateral field shadows represent axillary abscesses.<sup>2</sup>

With this résumé of anatomical characteristics of lung abscesses in mind we may go on to a consideration of each bronchopulmonary segment as it is concerned in the localization of lung abscesses. A series of 100 consecutive cases of acute lung abscesses was analyzed to determine the location of the lesions according to segments.



*Lower Lobe Apical Abscess (middle paravertebral abscess).*—The most frequent site of acute lung abscess is the lower lobe apical segment. This portion of the lung lies halfway between the top and bottom of the lung field and borders on the mediastinum and vertebral column. The bronchus supplying this segment points backward and inward and so determines the site of the abscess cavity which is found under the costal surface next to the spine. Fig. 2 shows the position of the shadow of a lower lobe apical abscess on an anteroposterior x-ray plate. The exact site of drainage is determined by measuring outward from the spinous process of the vertebra and downward by counting the transverse processes beginning at the first thoracic. These abscesses are erroneously called central abscesses. Actually, such abscesses always lie immediately under the costal surface of the lung as described. Fig. 3, IX shows diagrammatically the position in the lung substance in lateral and anteroposterior views that a lower lobe apical segment abscess assumes. Forty per cent of all acute lung abscesses appear in this segment (right or left side), thus simplifying the problem of localization considerably.

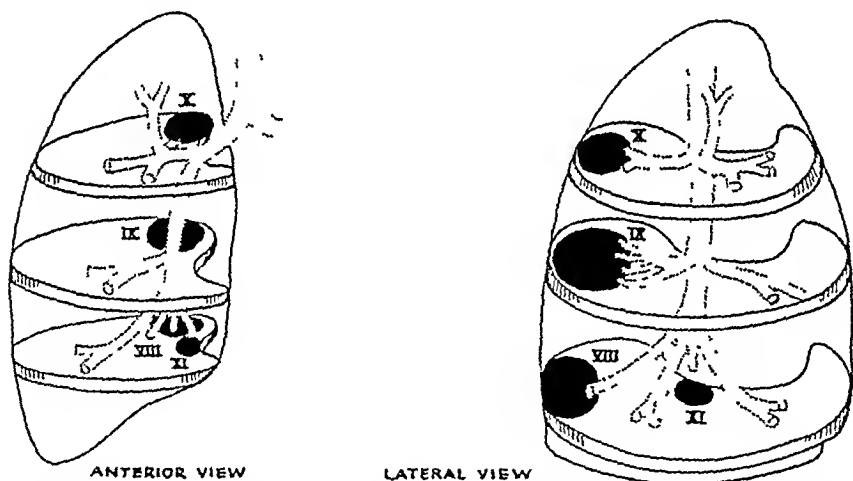
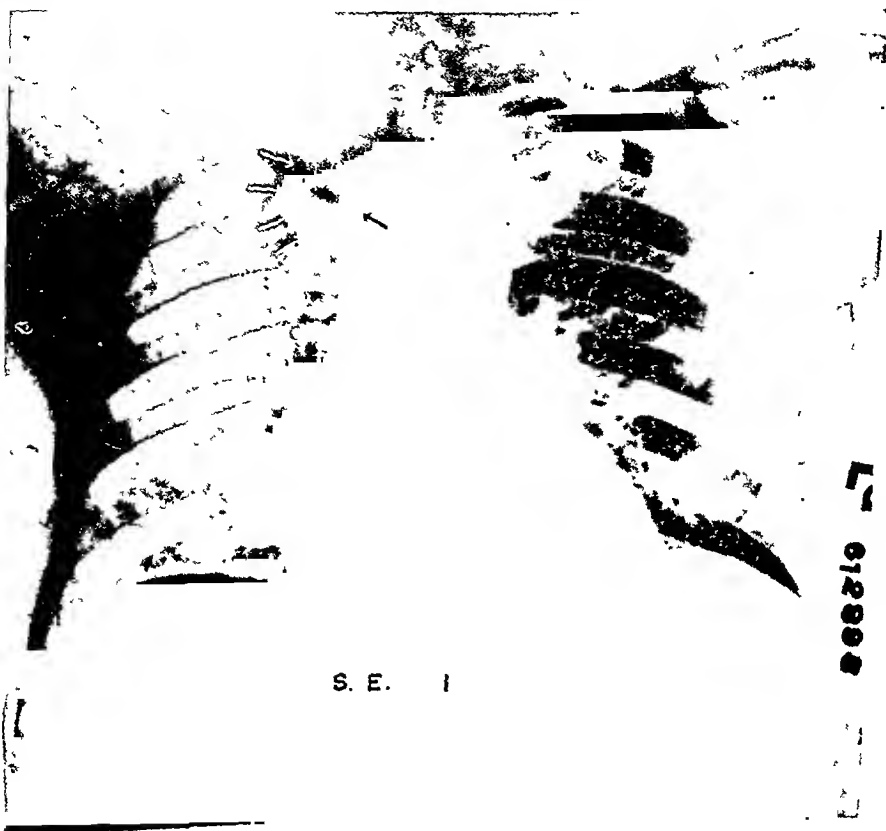


Fig. 3.—Right lung, anterior and lateral views. IX, Lower lobe apical segment (middle paravertebral) abscess. I, upper lobe paravertebral segment abscess. VIII, lower lobe paravertebral segment abscess. II, medial segment abscess.

*Upper Lobe Paravertebral Segment Abscess.*—Another frequent site of lung abscess is the upper lobe paravertebral segment. Fig. 1 shows the vertebral and costal surfaces and also the bronchus supplying this segment directed posteriorly and toward the vertebral column. This segment lies just above the lower lobe apical and the shadow of an abscess occupying this location lies in the upper part of the lung field next to the vertebral column (Fig. 1). The site of drainage is determined as in the previous segment and is usually about the level of the fourth thoracic transverse process. Eleven per cent of acute lung abscesses lie in this segment. Fig. 3, I shows diagrammatically the position in the lung

abscess, lateral and anteroposterior views, that an upper paravertebral segment assumes.

*Lower Lobe Paravertebral Segment Abscess.*—Continuing in the paravertebral region of the lung, we come to the lower lobe paravertebral segment. In addition to the paravertebral and costal surfaces, this segment has a diaphragmatic surface (Fig. 1). The bronchus supplying this segment is directed posteriorly downward and inward. Abscesses lying in this segment can always be reached directly through the posterior surface near to the vertebral column, although on rare occasions the pleural adhesions may be present only in the diaphragmatic surface. Six per cent of the cases lie in the lower lobe paravertebral pulmonary segment. Fig. 3, VIII shows the position that lower lobe paravertebral abscess assumes and Fig. 5 shows position on roentgenogram.



S. E. I

Fig. 4.—Position of upper paravertebral segment abscess in posteroanterior plate. This abscess must be drained posteriorly.

We see from preceding descriptions that the paravertebral segments, upper, middle, and lower, account for 57 per cent of all acute lung abscesses. These abscesses lie in the posterior part of the lung next to the vertebral column at the levels described and are represented on an

teroposterior x-ray by shadows lying in the medial lung field along the vertebral column shadow. Conversely, shadows lying along the vertebral column always represent abscesses in posterior segments. Lateral views always prove this, provided the abscess shadow can be distinguished from the bone of the vertebra.

The mesial segment (Fig. 3, XI) is the site of 3 per cent of the abscesses. This segment has only a mediastinal and diaphragmatic surface and its bronchus points downward. It lies halfway between the antero-posterior costal surface on the mediastinal aspect of the lung. This is the only site which cannot be drained directly through a costal surface



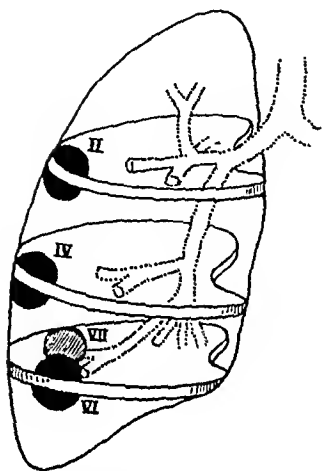
Fig 5—Lower lobe paravertebral abscess shadow. This abscess must be drained posteriorly.

and which requires a pushing aside of normal lung tissue in its drainage. It could conceivably, of course, be drained directly without traversing the free pleural cavity by incising upward through adhesions from the subdiaphragmatic space. So far this has not been attempted.

This abscess is about the same level as the lower lobe paravertebral abscesses, and at the medial part of the lung field the two sites cannot be distinguished in an anteroposterior x-ray and therefore require a

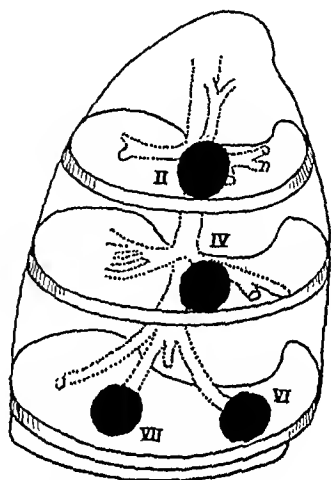
lateral x-ray for recognition. This will always show the mesial segment shadow midway between the anteroposterior surface of the chest abscess shadow midway between the anteroposterior surface of the chest.

*Lower Lobe Posterolateral and Anterolateral Segments.*—The lower lobe posterolateral and anterolateral segments in addition to axillary surfaces have diaphragmatic surfaces where sometimes adhesions take place. Even though this is the case, the lesion is still very close to the costal surface (within one-half inch) and can be drained without traversing normal pulmonary tissue.

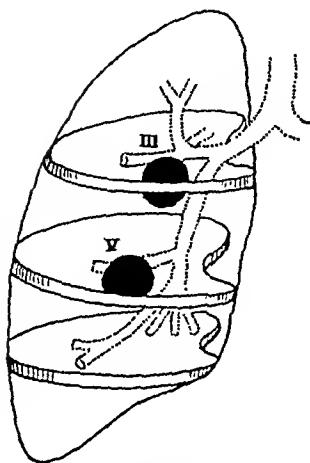


ANTERIOR VIEW

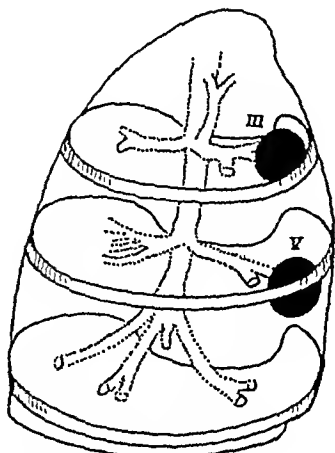
Fig. 6.—II, Upper lobe axillary; IV, middle lobe axillary; VI, anterolateral; VII, posterolateral.



LATERAL VIEW



ANTERIOR VIEW



LATERAL VIEW

Fig. 7.—III, Upper lobe, anterior; V, middle lobe, anterior.

The lower lobe posterolateral is the site of 9 per cent of acute lung abscesses and the anterolateral segment is the site of 4 per cent (Fig. 6, VI and VII).

*Middle Lobe Axillary and Anterior Segments.*—These segments make up 3 and 2 per cent respectively of acute lung abscesses (Fig. 6, IV, and Fig. 7, V). The anterior segment in addition to an anterior surface has a mesial one. Since its bronchus is directed anterolaterally, the lung abscess always lies under its anterior surface next to the ribs.

*Upper Lobe Anterior Segment.*—This segment accounts for 3 per cent of the acute lung abscesses. As Fig. 8 shows, it has an anterior and mesial surface; but, since its main bronchus is directed anterolaterally, the abscess cavity is found under the anterior surface (Fig. 7, III and Fig. 8).

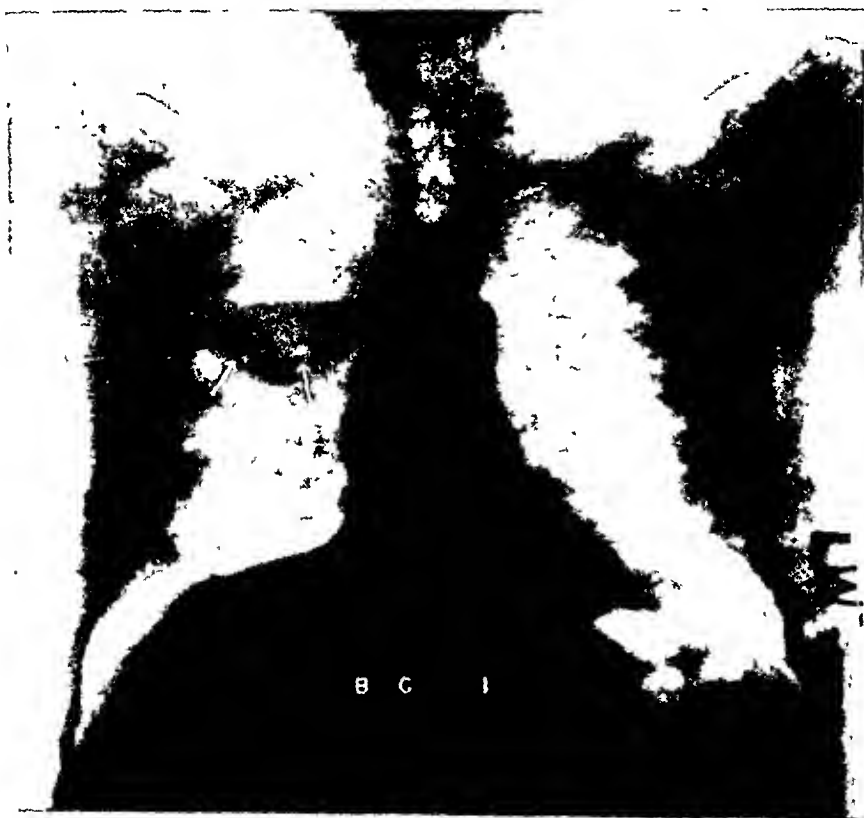


Fig. 8—Upper lobe anterior segment abscess. Approach is anterior.

*Upper Lobe Apical Segment.*—This segment, lying as it does at the top of the lung, is rarely involved by aspirated infected material. In this series of 100 cases it has been involved in one instance.

Table I is a summary of the segmented sites of acute lung abscesses in 100 cases.

#### COMMENT

The situation of an acute lung abscess within the pulmonary parenchyma is dependent on the course and position of certain lobar

TABLE I

RIGHT LUNG		LEFT LUNG	
Upper lobe		Upper lobe	
Anterior	3		0
Axillary	11		7
Apical	1		0
Paravertebral	9		2
Middle lobe		Anterior descending	
Anterior	2		1
Axillary	2		0
Lower lobe		Lower lobe	
Apical	22		18
Paravertebral	3		3
Posterolateral	3		6
Anterolateral	3		1
Mesial	3		0
Total	62	Total	38

Summary			
Lower lobe apical	(right and left)		40
Axillary	(right and left)		18
Anterolateral	(right and left)		4
Posterolateral	(right and left)		9
Upper lobe paravertebral	(right and left)		11
Lower lobe mesial	(right and left)		3
Lower lobe paravertebral	(right and left)		6
Middle lobe anterior	(right and left)		3
Middle lobe axillary	(right and left)		2
Upper lobe apical	(right and left)		1
Upper lobe anterior	(right and left)		3

bronchi which are anatomically constant. These bronchi, with their corresponding tissue, are designated as bronchopulmonary segments and are the lobar subdivisions on which the individual abscess is situated. Lung abscess occurs preponderantly in the paravertebral segments (57 per cent) and particularly in the middle paravertebral (lower lobe apical) segment (40 per cent). Gravity determines the segments most frequently involved. The lesion invariably is situated superficially within one of the lobes of the lung a short distance (within one-half inch) beneath the visceral pleura and usually facing the costal parietes. In the vast preponderance of cases the cavity can be entered directly through the overlying pleural adhesions and a thin shell of collapsed lung if the approach is made at the proper site. Lung abscess never lies in the center of the lobe and, if normal lung tissue is traversed in the surgical evacuation of the lesion, it must be concluded that the approach has not been made at the correct site.

#### SUMMARY AND CONCLUSION

1. The larger bronchi (subdivision of lobar bronchi) are constant in number and position.
2. The mass of pulmonary parenchyma aerated by each such subdivision has a constant shape, size, and position in the thoracic cage.

3. These bronchi with their corresponding parenchyma are known as bronchopulmonary segments.
4. The bronchopulmonary segments are units of clinical localization for lung abscess and other diseases due to aspiration such as bronchiectasis, bronchopneumonia, etc.
5. Bronchopulmonary segments are individually described.
6. A series of 100 cases of acute lung abscesses is analyzed according to bronchopulmonary segments involved and clinical location.

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# SIMULTANEOUS BILATERAL SPONTANEOUS PNEUMOTHORAX

A DISCUSSION OF ITS MECHANISM AND REPORT OF A CASE

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THE subject of bilateral pneumothorax has been repeatedly covered in the past. In the main, attention has been directed toward its incidence and its more frequent cause, viz., disease of the visceral pleura (Table I). It is the purpose of this communication to show that simultaneous bilateral spontaneous pneumothorax may follow operations not performed within the pleural cavity and may not be due to pleural disease. We will also discuss the mechanism of this type of spontaneous pneumothorax.

Oechsli and Miles<sup>20</sup> point out that instances of pneumothorax, excluding those that are traumatic and artificial, should be classified as spontaneous whether due to (1) some demonstrable pathologic change in the pleura which actually or presumably causes its perforation, (2) some cause that cannot be demonstrated, or (3) infection with a gas-producing organism. Olbrecht<sup>21</sup> reserves the term simultaneous bilateral spontaneous pneumothorax for those instances in which it occurs simultaneously or in which contralateral pneumothorax occurs before the original unilateral pneumothorax has disappeared.

The traumatic causes of pneumothorax, on the other hand, should be reserved for those cases where the injurious agent actually perforates the pleura. Such agents might be sword or bullet wounds, needle puncture, fracture of the rib, or direct forms of injury to the chest with disruption of the pleura. The cases we have collected from the literature and the one we are reporting represent instances of spontaneous pneumothorax that occurred without perforation of the pleura due to trauma or disease.

One mechanism by which spontaneous pneumothorax develops has been discussed by Sante,<sup>25</sup> Dorwart,<sup>5</sup> and Weinstein<sup>27</sup> and more recently demonstrated experimentally by Escudero and Adams.<sup>8</sup> In this type of spontaneous pneumothorax there is first partial atelectasis of a lung due to obstruction of a bronchus by mucus, such as may occur during or following anesthesia. If the diaphragm does not rise sufficiently, the mediastinum moves toward the affected side to neutralize the increased negative intrapleural pressure and the remaining lung becomes over-expanded. The pleura covering the now overdistended lung can rupture,



TABLE I

DISTRIBUTION OF 82 CASES OF SIMULTANEOUS BILATERAL SPONTANEOUS PNEUMOTHORAX\*

ETIOLOGICAL FACTOR	NO. OF CASES	APPROXIMATE PERCENTAGE
Pulmonary tuberculosis	39	48
Idiopathic	17	21
Emphysema	10	12
Pneumonoconiosis	7	9
Congenital cyst	3	3
Bronchopneumonia	2	2.5
Malignant tumor	2	2.5
Bronchiectasis	1	1
Interstitial fibrosis	1	1
Total	82	100

\*From Glickman and Schlomovitz.<sup>2</sup>

producing a pneumothorax. Escudero and Adams<sup>8</sup> reproduced such a course of events in dogs and in one instance produced a bilateral pneumothorax. Curiously enough they also demonstrated that in dogs, when pneumothorax was induced on one side, the air could diffuse through the mediastinum and enter the contralateral cavity.

Eliason and McLaughlin<sup>6</sup> report 120 cases with pulmonary complications out of 7,326 operations. Of these 120 patients with pulmonary complications there was only one instance of pneumothorax, but the type of operation and the details of the complication are not discussed in the article. Although these figures may give a clue to the incidence of pneumothorax as a postoperative complication, it might be overlooked or it might be confused or diagnosed erroneously as postoperative atelectasis, which is by far a more common complication. The case described by Dorwart<sup>5</sup> and the one discussed by Weinstein<sup>27</sup> are illustrative of the latter possibility.

Dorwart's<sup>5</sup> patient was doing fairly well after the removal of a stone from the right kidney and a heminephrectomy. Suddenly on the eleventh postoperative day the patient became cyanotic and anxious, while the respirations jumped to 38 and the pulse to 160 without cough or pain. Twelve hours later a diagnosis of right massive pulmonary atelectasis was made, but thirty-six hours later, when x-ray films of the chest were made, a right pneumothorax was discovered. Without specific treatment the pneumothorax was absorbed and twenty days later the lung was completely expanded. An x-ray film of the chest taken two years after this incident showed that the lung fields were clear and without evidence of pulmonary tuberculosis. Dorwart<sup>5</sup> believes that the pneumothorax was preceded by a partial atelectasis of the lung which led to the pressure changes that produced a bursting of the remaining overexpanded lung with the consequent pneumothorax.

The case reported by Weinstein<sup>27</sup> was that of a 42-year-old woman who had a cholecystectomy with exploration and drainage of the

common duct. While reacting from anesthesia, she coughed considerably, became moderately cyanotic, and had a great deal of mucus in her pharynx. The cyanosis disappeared, but the cough persisted and subsequently dyspnea and cyanosis reappeared. Signs of partial atelectasis of the right lung were reported, but on the seventh postoperative day an x-ray of the chest showed a right pneumothorax with some mediastinal displacement to the left. The pneumothorax was slowly absorbed and eight weeks later on x-ray examination there was moderate thickening of the pleura. Weinstein<sup>27</sup> believes that the pneumothorax resulted from the rupture of a subpleural bleb.

The second mechanism has been demonstrated clinically by Keis,<sup>16</sup> Wiethe,<sup>29</sup> Iglaue,<sup>11</sup> and both clinically and experimentally by Champneys.<sup>3</sup> This mechanism has been either disregarded or lost sight of for some time, although in the thirteenth edition of Osler's *Principles and Practice of Medicine*, Christian<sup>4</sup> mentions Champneys' experimental work as illustrating a cause of mediastinal emphysema.

To test out the efficiency of various types of artificial respiration, Champneys<sup>4</sup> did experimental tracheotomies on twenty-one stillborn infants and then performed artificial respiration. Mediastinal emphysema was noted in seven instances and of these five had a pneumothorax. In one experiment the pneumothorax was bilateral. Champney noted that in six of these seven cases showing mediastinal emphysema there was a sucking sound heard at the base of the neck about the tracheotomy wound. By continuing his observations and using colored fluids he was able to trace their course down into the superior mediastinum. He postulated two conditions that must be present to favor the production of mediastinal emphysema. The first is a wound of the deep cervical fascia, and the second is obstruction of the air passages with continuation of forced inspiratory movements. If the pressure in the mediastinum is equalized by removing the obstruction in the air passages, the emphysema does not progress. However, if the obstruction is not removed or forced, inspiratory movements continue; i.e., there is a continued marked difference between the atmospheric mediastinal and intrapleural pressure, the mediastinal parietal pleura ruptures, and air from the emphysematous mediastinum diffuses through, producing a pneumothorax.

From the records of St. Bartholomew's Hospital, Champneys found three autopsied cases of mediastinal emphysema following tracheotomy. A unilateral pneumothorax was present in one and a bilateral pneumothorax was present in a second case. One of these cases had subcutaneous emphysema. From 1860 until 1884 the records of the Hospital for Sick Children yielded eighty-two cases with autopsies following tracheotomy for various causes. Mediastinal emphysema was present in five cases; one had bilateral pulmonary collapse, and three had subcutaneous emphysema, but none was recorded as having had a

pneumothorax. He believed that the pneumothorax was probably missed in many instances because it was not expected and it was not particularly looked for. In a later publication from the same hospital ten additional autopsied cases of mediastinal emphysema were reported following tracheotomy and in two pneumothorax was found.

The experiments performed on rabbits by Ballou and Francis<sup>1</sup> may be interpreted as offering confirmatory evidence of this principle. A rubber balloon was placed in the mediastinum of living rabbits and the effects of variations in the mediastinal pressure were noted. They observed that pneumothorax developed when the increased mediastinal pressure was greater than the mediastinum could withstand. They also showed that mediastinal emphysema may be a consequence of a pneumothorax or a pneumothorax may be due to what was originally a mediastinal emphysema.

The earliest cases of pneumothorax following a surgical procedure are those mentioned by Wilks and Moxon<sup>29</sup> in their *Lectures on Pathological Anatomy*, in 1875, referred to by Champneys. They described two cases as follows: "We believe we have seen two cases of pneumothorax arise from tracheotomy and we mention the circumstances because we are not aware that it has ever been alluded to. In one case, where after tracheotomy, death occurred without sufficient reason, both lungs were found contracted in the chest and the cellular tissue in the posterior mediastinum was filled with air producing large bubbles, which we think had burst the pleura into the chest. In another case where most extensive superficial emphysema followed the operation, the breathing became laborious before death, and the lungs were found contracted in the same manner; the emphysema having penetrated the mediastina."

Iglauer<sup>11</sup> reported a case of low tracheotomy in a 23-month-old child. He noted a marked sucking noise at the base of the neck. At the conclusion of the operation, subcutaneous emphysema was present and an x-ray of the chest disclosed an almost complete right-sided pneumothorax. In a similar vein Leiner<sup>17</sup> reported twelve cases of tracheotomy in children in nine of which mediastinal emphysema ensued, but there were no cases of pneumothorax. Crepitation synchronous with the cardiac systole was the chief sign observed. Eight of the cases had subcutaneous emphysema.

Wiethe<sup>24</sup> added two cases of left-sided pneumothorax in children following low tracheotomy. Both cases survived. He made further anatomical observations on post-mortem material, but his explanation of the mechanism of the pneumothorax was that of laceration of the left pleural dome during operation, thus favoring a traumatic cause for the pneumothorax.

Mediastinal emphysema with pneumothorax may follow thyroidectomy, particularly when sub-sternal portions of the gland are removed.

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was attributed to the rupture of another emphysematous bleb from the postoperative coughing.

Although the above explanation may be correct, another mechanism is rupture of the diaphragmatic peritoneum with the development of mediastinal emphysema by aspiration of air through the crus of the diaphragm. Sufficient surgical injury to the retroperitoneal tissues may have occurred during the operation to permit the aspiration of air, particularly when it is considered that there had been respiratory difficulties during the operation. Similar cases have been reported in the literature. Ritter<sup>24</sup> described subcutaneous emphysema of the head and neck following excision of a gastric ulcer. Jessup<sup>25</sup> described a fatal case of mediastinal emphysema following splenectomy, during which the diaphragm was incised and repaired. No pneumothorax was observed at the autopsy. Newman<sup>19</sup> reported a case of generalized emphysema first appearing at the jugulum following a rupture of the stomach. Erichsen's patient<sup>7</sup> developed subcutaneous emphysema after the bladder had been punctured through the rectum for acute urinary retention, although from the clinical description one may assume that the patient may have had a gas bacillus infection. A similar case was reported by Tatum.<sup>26</sup> Pearce<sup>22</sup> described a case in which perforation of the esophagus was associated with an abscess of the cardiac end of the stomach. The patient died from subcutaneous and mediastinal emphysema with bilateral pleural effusion.

#### CASE REPORT

The case which we wish to present is that of a 57-year-old white male, a painter by occupation, who first applied at the Memorial Hospital Clinic on Sept. 28, 1938, at which time he complained of hoarseness and cough of sixteen months' duration. The family history was irrelevant. There was nothing in his past history suggesting antecedent pulmonary infection and there were no pulmonary symptoms suggestive of emphysema at the time of admission to the clinic. He was a heavy user of tobacco.

Physical examination disclosed a tumor of the left vocal cord with fixation of the structure. The remainder of the physical findings were within normal limits.

A biopsy of the left vocal cord was reported as epidermoid carcinoma, Grade II. Wassermann and Kahn tests were negative. Blood chemistry studies were within normal limits and a roentgenogram of the chest was normal.

Inasmuch as the lesion was limited to the intrinsic larynx a total laryngectomy was done on October 31, 1938, under local anesthesia. A permanent tracheal opening was left at the root of the neck in the midline.

Beyond a transitory pharyngeal fistula and low-grade cellulitis of the neck, the postoperative convalescence was uneventful. The patient was discharged on the fiftieth postoperative day.

Gross and microscopic studies corroborated the biopsy.

He remained free of disease until September, 1939, when a metastatic node was found in the lower left cervical region. He was readmitted to the hospital for a radical neck dissection. On Sept. 29, 1939, a radical neck dissection was done under local anesthesia. Due to the fact that the patient already had a tracheotomy, it was necessary to suture a tube in place in the tracheal stoma in order to cover

Keis<sup>16</sup> describes a case in which a thyroid tumor was removed under general anesthesia. There was a period of dyspnea during the operation. Without further details Keis states that the patient died. Autopsy showed a mediastinal emphysema with bilateral pneumothorax. There was no demonstrable pleural injury or pulmonary disease. He collected seven other cases from the literature where mediastinal emphysema followed thyroidectomy. In four of these cases a bilateral pneumothorax was demonstrated at autopsy and no injury to the pleura was observed. From Keis' bibliography we have located three of these cases. Jehn and Niessen's<sup>17</sup> patient developed respiratory symptoms within one hour after the operation. Gold<sup>18</sup> reported four cases of mediastinal emphysema following thyroidectomy, one of which showed subcutaneous as well as bilateral pneumothorax. During the operation on this patient a hissing noise was heard at the base of the neck. Lotheisen's<sup>19</sup> case had malignant struma with severe tracheal stenosis. Five days after partial thyroidectomy, a tracheotomy was performed and a hissing sound of aspirated air was heard before the tracheotomy was completed.

Jessup<sup>15</sup> in a review of the subject of mediastinal emphysema lists six pathways in order of their frequency by which air may get into the mediastinum: (1) the pulmonary interstitial tissue extending along the peribronchial and perivascular connective tissue to the hilus, thence diffusing into the loose areolar tissue of the mediastinum; (2) extension of a subcutaneous emphysema along the endothoracic fascia at the jugulum; (3) the direct sucking of atmospheric air through wounds in the superior and inferior apertures of the thorax; (4) injury of the trachea and main bronchi whereby air is blown directly into the mediastinum; (5) openings in the mediastinal pleura so that air produced by pneumothorax is admitted; and (6) extension of retroperitoneal emphysema through the crura of the diaphragm.

The case reported by Phillips, Waldron, and Vanzant<sup>23</sup> may be illustrative of the sixth pathway mentioned above. The patient was a white male, aged 29 years. A subtotal gastric resection with Polya anastomosis was performed for perforating duodenal ulcer. The patient did not take the gas-ether anesthesia well and at the end of the operation there was noticeable subcutaneous emphysema in his neck with dyspnea and cyanosis. The emphysema continued to increase. On the next day a film of the chest showed a right partial pneumothorax. There was a stormy postoperative course with a good deal of coughing. A roentgenogram taken on the eleventh postoperative day showed a bilateral pneumothorax that was complete on the right and partial on the left.

The authors presume that there were bilateral emphysematous blebs and, following the strain of anesthesia, one of these ruptured on the right side, resulting in a pneumothorax which was accompanied by a passage of air up through the mediastinum into the neck and over the chest, producing the subcutaneous emphysema. The left pneumothorax



this area with sterile drapes. The dissection was carried out from below upward. The sternal and clavicular insertions of the sternocleidomastoid muscle were severed early in the operation and the internal jugular vein was taken along with the muscle. The metastatic node was removed with these structures. During this time the patient had no difficulty breathing. However, during the latter part of the operation when the dissection was being carried out in the upper portion of the left neck, the patient experienced gradually increasing dyspnea. Coincidentally, there



Fig. 1.—Sept. 30, 1939. Film showing bilateral pneumothorax. Apex and base involved in right side and apex involved in left side.

was a loud sucking noise heard in the left supraclavicular fossa and the tissues in this area alternately rose and fell with each respiratory excursion. Attempts to relieve the patient by rearranging the drapes and administering oxygen through the tube were only partially successful.

He was returned to the ward after the completion of the operation. At that time he was quite cyanotic and dyspneic with a respiratory rate of 30. Three hours postoperatively his condition was poor. He complained continually of a squeezing



pain in the lower sternal and epigastric areas and he was in mild collapse. There was moderate cyanosis despite the continuous administration of oxygen through the tracheotomy tube and his face was somewhat puffy. The respiratory excursions were increased in rate and depth. There was subcutaneous emphysema over the right upper anterior chest.

Percussion over the left hemithorax and right anterior chest showed hyperresonance. Over the right posterior chest the note was tympanic. The breath sounds were questionably audible over the upper four fifths of the chest. Posteriorly at the bases there was a transverse bandlike area where the breath sounds were more easily heard but they were still distant. Expiration was prolonged.

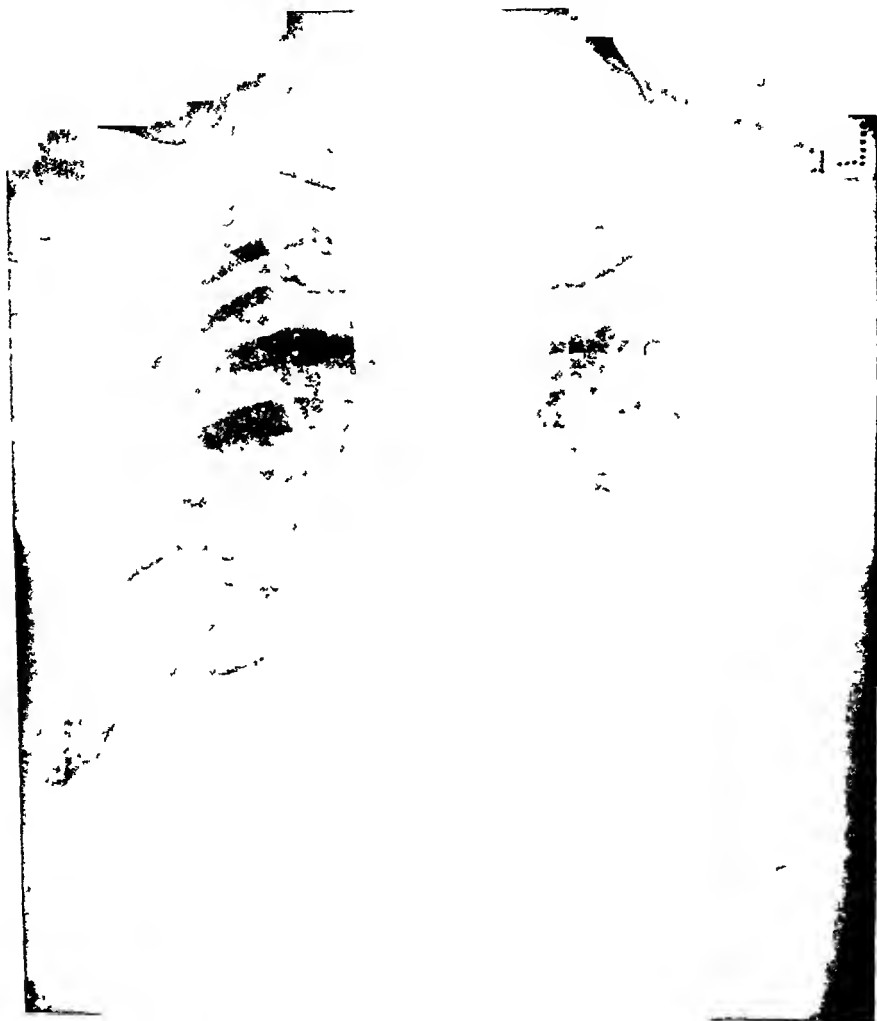


Fig 2—Oct 9, 1939. Film of chest showing bilateral pneumonitis of lower lung fields. Pneumothorax has completely disappeared.

The pulse rate was 88 with occasional extrasystoles. The blood pressure was 128/80. The area of cardiac dullness was obscured by the hyperresonance of the left chest. The heart sounds were barely audible and there was a faint crackling sound that was synchronous with each systole.

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By Oct. 2, 1939, the patient was over the acute features entirely except for some mild hyperpnea. The subcutaneous emphysema increased moderately over the right anterior chest, but later it was gradually absorbed.

His convalescence was complicated by an erysipeloid infection of the wound and a bilateral pneumonitis of a mild degree (Fig. 2). By the twentieth postoperative day the patient was clinically well and a film of his chest showed no evidence of any abnormality (Fig. 3). He was discharged on the twenty-third postoperative day.

In December, 1939, the patient had a plastic operation for stenosis of the tracheal stoma. There were no complications associated with this operation. A month later there was no evidence of any effects from the pneumothorax which was completely absorbed. He has subsequently remained well.

In the consideration of the development of the pneumothorax of this patient there are several salient features which should be emphasized. First, there was the obvious difficulty of breathing with strong inspiratory efforts. This condition was accompanied by a loud sucking noise in the left supraclavicular fossa. Direct injury to the pleura might be regarded as the cause of the dyspnea and the pneumothorax, but it must be borne in mind that the symptoms and sucking sound first occurred toward the end of the operation when the dissection was being carried out on the upper part of the neck.

It would seem more likely that some partial mechanical obstruction to the patient's air supply occurred late in the operation, possibly through disarrangement of the drapes or compression of the oxygen supply tube. In either event, there was sufficient air hunger to produce dyspnea with strong inspiratory efforts. This corresponds to Champneys' first requirement for the development of mediastinal emphysema. A sucking noise was heard in the left supraclavicular fossa and this observation was also made in cases reported by Champneys,<sup>3</sup> Iglaue,<sup>11</sup> Wiethe,<sup>12</sup> Gold,<sup>13</sup> Lotheisen,<sup>14</sup> and Buford.<sup>2</sup> Wiethe points out that this sucking sound may be confused with aspiration of air into the veins and, in fact, such a complication was considered in the case which we have described. However, since hemostasis was complete in the lower cervical region, other causes for the noise were considered.

Champneys' second cause for the development of mediastinal emphysema, a wound in the deep cervical fascia, was more than fulfilled in this case, since a portion of the deep cervical fascia was removed with the specimen. We are thus of the opinion, in accordance with the experimental findings of Champneys, that, because of the violent inspiratory efforts of the patient, air was drawn into the mediastinum through the defect in the deep cervical fascia. The patient continued his inspiratory efforts for twenty minutes or longer. Apparently, sufficient difference in pressure between the mediastinum and pleural cavity resulted to permit the rupture of the mediastinal pleura on both sides with the production of a bilateral pneumothorax.

The abdomen was distended without tenderness or rigidity.

An electrocardiogram showed normal sinus rhythm, normal PR and QRS conduction time. There was no evidence of coronary occlusion.

A clinical diagnosis of bilateral spontaneous pneumothorax with mediastinal emphysema was made.

The patient was treated expectantly with supportive measures and in a few hours he was much more comfortable.

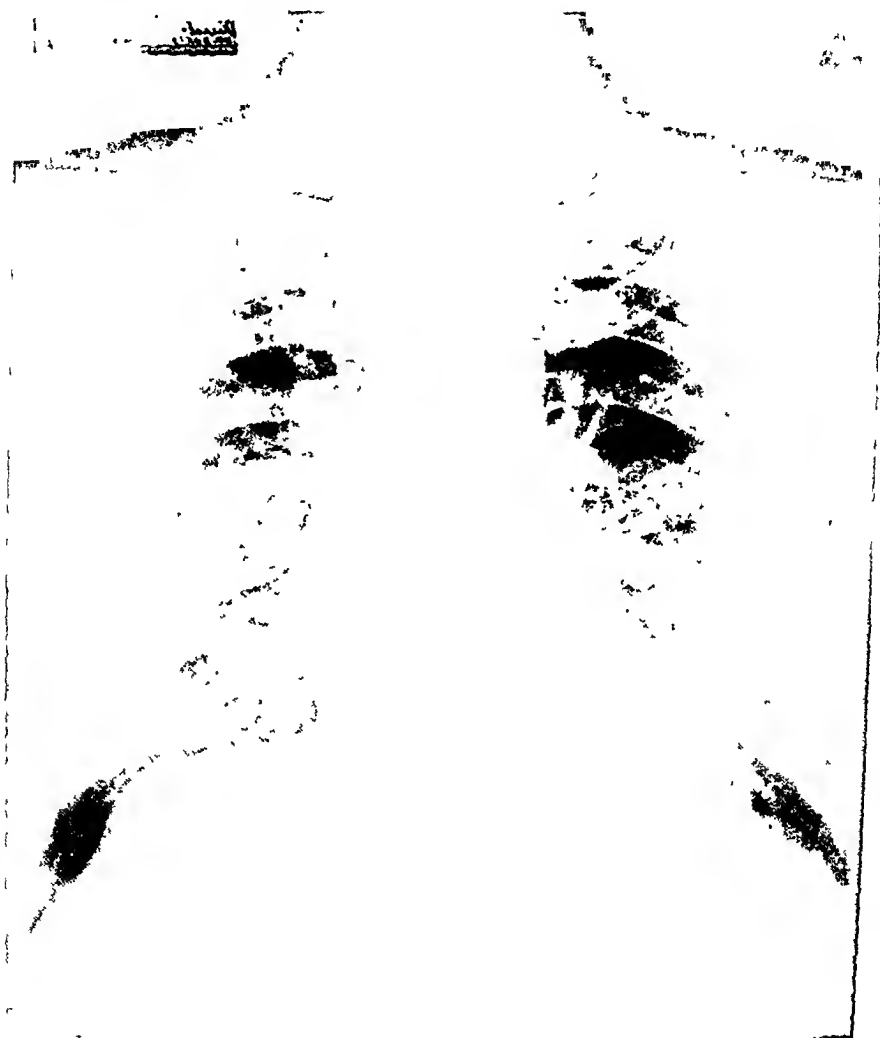


Fig. 3.—Oct. 19, 1939. Film showing return to normal

The next morning, Sept. 30, 1939, there was clinical evidence of increasing expansion of both lungs at the bases, but no breath sounds were audible over the upper one third of either lung field. At the same time a chest film showed a bilateral partial pneumothorax which was more marked on the right side than on the left (Fig. 1).

From the literature we have collected eighteen cases of spontaneous pneumothorax that followed operations: Wilks and Moxon, Champneys, Iglauer, Wiethe, Keis, Jehu and Niessen, Gold, Lotheisen, Dorwart, Phillips, Waldron and Vanzant, Weinstein, and Eliason and McLaughlin. Six of these cases had unilateral pneumothorax: Champneys, Iglauer, Dorwart, Wiethe, and Weinstein. Nine cases had bilateral pneumothorax: Wilks and Moxon, Champneys, Keis, Phillips, Waldron and Vanzant, Jehu and Niessen, Gold, and Lotheisen. In three cases the type of pneumothorax was not stated. In six cases the pneumothorax may be considered the cause of death: Wilks and Moxon, Champneys, Keis, Jehu and Niessen, and Gold. Six cases recovered from the pneumothorax: Iglauer, Wiethe, Dorwart, Phillips, Waldron and Vanzant, and Weinstein, while in the remaining six cases neither the cause of death nor the end result was clearly described.

### CONCLUSIONS

Spontaneous pneumothorax as a postoperative complication is probably more common than is suspected because it may be overlooked or confused with other postoperative pulmonary or cardiovascular conditions.

Besides the usual signs of pneumothorax, one should look for subcutaneous and mediastinal emphysema.

Pulmonary effort appears to be the principal factor in the production of the complication. This may occur during or after the operation.

The morbidity of the complication is difficult to state because all the cases were not clearly reported, but six out of nineteen patients died as a result of pneumothorax.

After a correct diagnosis has been made, the treatment should be directed toward supportive measures and, if necessary, aspiration of the pneumothorax should be performed.

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Besides the signs of bilateral pneumothorax the patient had subcutaneous emphysema. This was noted in cases reported by Wilks and Moxon,<sup>20</sup> Champneys,<sup>3</sup> Iglaue,<sup>11</sup> Gold,<sup>10</sup> Phillips, Waldron, and Vanzant,<sup>24</sup> and Buford.<sup>2</sup> However, subcutaneous emphysema without pneumothorax is not at all uncommon after operations about the root of the neck.

We also observed the sign emphasized by Leiner;<sup>17</sup> that is, a crackling sound synchronous with cardiac systole, supposedly indicative of mediastinal emphysema. It is conceivable that this could be produced by the contraction of the heart against a partially collapsed left lung.

The pain experienced by the patient was no more unusual than that seen in spontaneous pneumothorax resulting from other causes. Its location suggested the possibility of a coronary occlusion, but immediate and successive electrocardiograms failed to disclose any evidence of myocardial infarction. There were progressive changes noted in the electrocardiograms, but these can be explained by displacement and rotation of the heart with its subsequent return to its normal position. Buford's patient,<sup>2</sup> however, had mediastinal and subcutaneous emphysema following a thyroidectomy, but pneumothorax was not observed and no x-rays were taken. In addition, his patient had great precordial fullness and precordial pain with each inspiration. The symptoms were greatly accentuated by deep breathing, which was characteristic of our case. According to Jessup<sup>15</sup> the outstanding effect caused by mediastinal emphysema is a mechanical interference with circulation brought about by a compression of the large veins entering both sides of the heart. The clinical and experimental observations of Jehn<sup>12</sup> and Niessen<sup>14</sup> on mediastinal emphysema confirm this conclusion. A case is reported by Jehn<sup>12, 13</sup> in which the mediastinal emphysema was so great that very little blood was found in the cardiac circulation because of the compression of the great veins entering the heart.

We do not believe that this occurred in this case since there was no appreciable engorgement of the cervical or brachial veins and the electrocardiograms did not suggest myocardial anoxemia.

#### SUMMARY

A case is described of spontaneous bilateral pneumothorax accompanied by mediastinal and subcutaneous emphysema. These complications developed during a radical neck dissection and were caused by strong inspiratory efforts of the patient, according to a mechanism suggested by the experiments of Champneys. This mechanism must be distinguished from that of Sante's, Dorwart's, and Escudero and Adams', where the pneumothorax results from the rupture of the overdistended portion of the lung after massive collapse of another portion of the same lung. The patient reported made a satisfactory recovery without other than supportive treatment.

## Editorials

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Dr. Meyer Bodansky

(1896-1941)

**D**R. MEYER BODANSKY (member of the Editorial Staff of SURGERY), Professor of Pathological Chemistry at the University of Texas School of Medicine, died after a short illness at the John Sealy Hospital, Galveston, Tex., on June 14, 1941. He was born in Russia in 1896 and was brought to America by his parents in 1907. He received his Bachelor of Arts degree from Cornell University in 1918, his Master of Arts degree from the University of Texas in 1922, his Doctor of Philosophy degree from Cornell in 1923, and his Doctor of Medicine degree from the University of Chicago in 1935. During the World War he served in the laboratory division of the Medical Corps. He was instructor and adjunct professor in biological chemistry at the University of Texas from 1919 to 1925. He taught at Leland Stanford University from 1925 to 1926, returning to the University of Texas in 1926, where in 1930 he was made Professor of Pathological Chemistry, a position held until his death, except for one year as visiting professor at the American University at Beirut, Syria, 1922 to 1923. Dr. Bodansky directed the laboratories of the John Sealy Hospital and the John Sealy Research Laboratory.

Dr. Bodansky's research work and writings in physiologic chemistry are widely known and highly respected. His thesis on "The Chemistry of Heart Action" was an outstanding contribution. His textbook *Introduction to Biological Chemistry* is a standard text and is used in medical schools and graduate schools of medicine throughout the world. Other of his widely used books are *Introduction to Physiological Chemistry* and *Laboratory Manual of Physiological Chemistry*. In addition to his many activities, he contributed freely to scientific medical journals, chief of which were SURGERY, *The Journal of Biological Chemistry*, and the *American Journal of Physiology*.

He was a member of the American Society of Biological Chemists, The Society of Experimental Biology and Medicine, the A.A.A.S., American Society of Clinical Pathology, the Texas Academy of Science, and Sigma Chi.

Dr. Bodansky's death was more tragic because it occurred at the height of his productive activity. In addition to being laboratory director, teaching, and doing research work, he was preparing a new edition of his textbooks. With his many achievements he remained

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The guide in these procedures was the familiar preservation of normal or tumor tissues at ice box temperature for weeks or months, apparently without harm. The imitation of these conditions in parts still attached to the body is essentially bound up with the use of a tourniquet, which serves the double purpose of enabling the local part to be chilled thoroughly and accurately and preventing chilling of the rest of the body. After very many experiments in different animal species had demonstrated the retention of both vitality and healing power without any perceptible impairment, the radical proposal still aroused natural misgivings in conservative surgeons. Accordingly it was necessary for Allen to make the first trials on private patients, by taking personal charge and responsibility for the anesthesia. It became possible thus to announce a small series of encouraging experiences.<sup>4</sup> Through Homer Cudmore the method was brought to the attention of Lyman W. Crossman, under whose direction it has since been used on the surgical service at City Hospital, New York City, with participation by W. F. Ruggiero, Vincent Hurley, and other associates, and the helpful cooperation of the heads of other services. The principal experience to date has consisted of amputations for peripheral vascular disease and its complications, but it is expected that reports on other uses will be made subsequently by different staff members.

A series of about forty amputations up to the present cannot be made a basis for too positive claims, especially as the early technique was primitive and greater accuracy and efficiency are expected from the apparatus only now becoming available. Nevertheless it is necessary to state impressions and reasons why the method should be used even experimentally. The following may therefore serve as a summary of the advantages according to preliminary impressions and hopes, subject to any necessary amendments with larger experience: (a) simple and efficient anesthesia, differing from other methods in being an anesthesia of protoplasm as well as of nerves; (b) accordingly, absence of all the usual signs or symptoms of shock; (c) reduced liability to pain, edema, infection, and necrosis, with the aid of postoperative cooling; also freer drainage when necessary; (d) consequently, success sometimes at lower levels of amputation than formerly considered feasible; (e) for all these reasons, lower mortality; (f) slower but healthier healing processes, and better average character of the final scar and stump.

The more limited the circulation, the more completely a limb can be chilled through and through without a tourniquet; therefore theoretically bacterial activity should be arrested more effectively in an arteriosclerotic than in a normal limb, and the local tissue metabolism should be capable of reduction to a level for which the existing blood supply is adequate. This principle seems to succeed in practice to the extent that an advancing arteriosclerotic gangrene can be delayed and

modest and retiring to the extreme. He was kind and sympathetic, and a faithful friend to all his associates and students. He was highly respected by all who knew him and admired by scientists of the medical profession everywhere. His passing is a serious loss to his institution, as well as to medicine and allied sciences.

—*Albert Singleton, M.D.*

Galveston, Tex.

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### Reduced Temperatures in Surgery

VARIOUS external uses of cold in the form of water, ice, ice bags, and other applications belong to the immemorial traditions of medicine and surgery. New ideas have developed in recent years along two independent lines.

The bold pioneer work of Temple Fay, now gaining more deserved recognition, comprised essentially two innovations: one, radical and prolonged local chilling by means of refrigerating tubes and capsules introduced directly into the tissues; the other, the artificial reduction of general body temperature to levels not previously considered possible in man, maintaining during several days a bodily and mental state which has been compared with the hibernation of lower animals. These methods and the fundamental physical and biological principles upon which they were based became associated in the medical mind almost entirely with the attack upon cancer; but regardless of what may prove to be the ultimate value in this field, Fay has pointed out additional uses ranging from the treatment of infections as serious as brain abscess and gas gangrene to the relief of pain and other neurologic and psychiatric disorders.<sup>1</sup> In Fay's own field of neurosurgery there appear to be fascinating theoretical possibilities that inflammatory reaction may be checked, edema controlled, and the consistency of the nervous tissues made firmer by low temperature so as to facilitate handling and reduce lacerations.

The other line of development, less known and therefore requiring fuller explanation, originated from the problem of diabetic or arteriosclerotic gangrene. States of insufficient circulation were studied through experiments on tissues or organs without any circulation, primarily on animals' legs deprived of blood supply by a tourniquet. It was found that heat markedly accelerated necrosis, while cold permitted the survival of the legs for at least fifty-four hours<sup>2</sup> and of rats' tails for more than ninety-six hours.<sup>3</sup> Shock, thrombosis, and damage to vessels or nerves were also strongly inhibited by cold. These facts, together with the well-known restraint of bacterial activity by reduced temperature, suggested practical applications to treatment.

The guide in these procedures was the familiar preservation of normal or tumor tissues at ice box temperature for weeks or months, apparently without harm. The imitation of these conditions in parts still attached to the body is essentially bound up with the use of a tourniquet, which serves the double purpose of enabling the local part to be chilled thoroughly and accurately and preventing chilling of the rest of the body. After very many experiments in different animal species had demonstrated the retention of both vitality and healing power without any perceptible impairment, the radical proposal still aroused natural misgivings in conservative surgeons. Accordingly it was necessary for Allen to make the first trials on private patients, by taking personal charge and responsibility for the anesthesia. It became possible thus to announce a small series of encouraging experiences.<sup>4</sup> Through Homer Cudmore the method was brought to the attention of Lyman W. Crossman, under whose direction it has since been used on the surgical service at City Hospital, New York City, with participation by W. F. Ruggiero, Vincent Hurley, and other associates, and the helpful cooperation of the heads of other services. The principal experience to date has consisted of amputations for peripheral vascular disease and its complications, but it is expected that reports on other uses will be made subsequently by different staff members.

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the local color temporarily improved; also a threatening infection can sometimes be checked as regards local symptoms and systemic absorption. Thus far in the experience with peripheral vascular disease these benefits have not extended to the point of a cure by conservative treatment. The patient may be saved in the sense of bringing him into condition to be cured by operation, but as yet the necessity of operation has not been obviated.

The immediate and positive value for the control of pain, shock, and infection strongly recommends this method for traumatic and military surgery. The requisite apparatus for dispensing with the use of ice need not add greatly to the load of a truck or ambulance. Patients with all sorts of limb wounds can thus be transported, or their treatment can be delayed for any emergency reasons, for at least several hours without hemorrhage, pain, shock, growth of gas-forming or other organisms, and also without the harm resulting from a tourniquet at ordinary temperatures. At the end of this time they are ready for operation without an anesthetic and without any added shock. Existing conditions seem to make this one of the most urgent fields for further research.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BIALOCK, M.D.

## SULFANILAMIDE AND ITS DERIVATIVES IN SURGICAL INFECTIONS

### A REVIEW

#### I. THE MODE OF CHEMOTHERAPEUTIC ACTION OF THE SULFONAMIDES\*

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#### MODE OF ACTION

THE earliest observations on the mode of action of the sulfonamides were made largely by clinicians, some of whom conducted laboratory studies supplementing investigations of the therapeutic effectiveness of sulfanilamide in hemolytic streptococcal infections. Leonard Colebrook,<sup>1</sup> who published the first statistically significant clinical report on any of the sulfonamides, one dealing with puerperal sepsis, observed (1936) that "p-aminobenzene sulfonamide (sulfanilamide) has a bacteriostatic and bactericidal action against small numbers of hemolytic streptococci in culture medium and in blood. Following administration of the sulfonamide . . . to man and animals their blood is bactericidal to hemolytic streptococci." It therefore became apparent five years ago that the search, initiated by Paul Ehrlich, for a drug which would be relatively nontoxic for animals and man, and would act upon bacteria in vivo as well as in vitro, had been successful. Study of the peritoneal exudates of infected mice under treatment with sulfanilamide led a number of investigators<sup>2, 3a</sup> into substantial agreement that sulfanilamide brought about a restriction in the capacity of invasive bacteria to multiply within the body and, in addition, probably rendered the surviving bacteria more susceptible to destruction by the phagocytes of the host.

Marshall and his co-workers<sup>4</sup> brought out the fact that sulfanilamide administered to animals and man becomes distributed with remarkable uniformity throughout the body fluids and the tissues bathed by these fluids. It thus appeared probable that the administration of sulfanilamide contributes toward producing a generalized elevation in the bacteriostatic capacity of all of the intra- and extracellular fluids of the body. However, Colebrook himself pointed out that the demonstration

\*Part II will appear in a subsequent issue.

of the production by sulfonamides of *bacteriostasis* in vivo was not alone enough to constitute an explanation of the mode of action of the drug in terms capable of being put to practical use in the further development of chemotherapy. It was quite essential to determine precisely how the sulfonamides bring about their interference with the customary growth activity of invasive bacteria. The first step in the development of present concepts of the mode of action of the sulfonamides was through the accumulation of data concerning the factors which tend to increase or diminish the magnitude of the effect of the drug in vitro and in vivo. The present review will show that the evidence so obtained pointed to the fact that the action of the sulfonamides was probably to disturb the operation of an enzyme system upon which the continuation of bacterial multiplication depends. It was then possible for students of the chemistry of bacterial metabolism to approach identification of the particular enzyme system involved.

#### FACTORS CONDITIONING THE MAGNITUDE OF THE DRUG EFFECT

1. *Ratio Between Concentration of Drug and Number of Bacteria.*—Colebrook<sup>5</sup> noted that "the growth of small inocula of streptococci in culture medium is inhibited by minute quantities of the sulfanilamide, but with large inocula there is no effect, even with a concentrated solution." The importance of the concentration of the drug is obvious and requires little elaboration. Most of the experimental data bearing on this point suggest that the production of bacteriostasis depends upon the existence of a quantitative relationship between the molecular concentration of sulfonamide on the one hand, and the number of bacteria on the other, provided, of course, that the composition of the medium, the temperature, and the age and strain of the culture are controlled. However, the molecular concentration obtainable with any given drug is limited by its solubility; whereas, the number of bacteria and the other factors are subject to wide variation. No agreement has developed among investigators as to the quantitative aspects of the drug-bacteria ratio because, with few exceptions, no two individuals have employed identical conditions for studies in vitro. It is of practical importance to recognize, however, that altering the concentration of the drug induces variations of far less magnitude than altering the composition of the medium or the temperature of incubation. Complete failure of therapeutic response in an infection seems less often to be due to inadequate concentration of drug than to an unfavorable adjustment of other conditions; e.g., a drug-resistant species, or substances in the inflammatory zone which would tend to antagonize the effect of any concentration of drug which might be obtained.<sup>6</sup>

2. *Nutrient Properties of the Medium.*—In 1938 Lockwood<sup>7</sup> called attention to the fact that the inhibitory effect of sulfanilamide on the growth of hemolytic streptococci in human serum was largely removed by the addition to the serum of small amounts of commercial peptone.

Since only the virulent variants of the strains of streptococci which were used showed a capacity to grow in peptone-free human serum, it was suggested that the effect of sulfanilamide might be to prevent operation of an enzyme system necessary to bacteria in splitting or in utilizing the protein substrate. This effect might be of critical importance in a medium such as peptone-free serum, wherein the sources of nitrogen are chiefly in the form of undegraded protein. Once the bacteria ceased multiplying they underwent disintegration and autolysis. The lethal action of the drug upon bacteria was therefore believed to be not a phenomenon of active sterilization, but a subtle interference with an integral nutritive process, leading to death of the cells by "starvation." The addition of peptone offered the bacteria an alternative source of nitrogen, permitting their escape from the bacteriostatic action of the drug. In an effort to account for the failure of concentrated solutions of sulfanilamide to destroy large inocula of streptococci in serum, the author observed that "the death and dissolution of some of the organisms may provide the more resistant survivors with split-products of bacterial proteins which they may utilize instead of serum protein." Although many investigators have confirmed the observation that the bacteriostatic action of sulfanilamide is limited by the presence in the medium of products of the enzymatic degradation of protein,<sup>8, 9</sup> a good deal of doubt has been cast on the validity of the hypothesis which Lockwood advanced, particularly as it related drug action specifically to the protein-splitting activity of bacteria. Fuller, Colebrook, and Masted<sup>10</sup> were unable by direct methods to detect any effect of sulfanilamide on the weak proteolytic activity of hemolytic streptococci. They also noted that sulfanilamide was active in their peptone-containing medium, and that the addition of serum, which afforded better conditions for streptococcal growth, interfered with the drug effect. Meanwhile, White and Parker<sup>11</sup> published evidence that the bacteriostatic action of sulfanilamide on streptococci was greatly enhanced if the temperature was raised above the optimum for the culture, and that small inocula of streptococci would die out in sulfonamide-containing media at 39°, whether they contained peptone or not. Gay, Clark, Street, and Miles<sup>12</sup> and Weld and Mitchell<sup>13</sup> advanced the view that environmental factors favorable to the bacteria would limit sulfonamide bacteriostasis, and that maximal drug effects are obtainable only in deficient media. According to this concept, peptone interferes with sulfanilamide in a serum medium only by "stimulating" the growth of the streptococci (or other species), and the mutually antagonistic effects of sulfanilamide and peptone are nonspecific, instead of specific, as suggested by Lockwood. However, since other substances which accelerate the growth of streptococci in serum, such as dextrose,<sup>3b</sup> and acid-hydrolyzed peptone<sup>14</sup> fail to antagonize sulfonamide bacteriostasis, and since cultures which have ceased multiplying in sulfanilamide-containing media may be returned to growth activity by the addi-

tion of peptone,<sup>7</sup> there remains the definite probability that commercial peptone, or one of its components, is a specific inhibitor of sulfanilamide action in biologic fluids.

In any event, experimental evidence as indirect as that reviewed up to this point could at most be only suggestive of the nature of the mechanism of the action of the sulfonamides and may not be employed as final proof of any hypothesis. The emphasis upon the nutritional environment of the bacteria in relation to their susceptibility to sulfonamide action had the effect of stimulating further work along similar lines.

Stamp<sup>15</sup> applied himself to a search for other substances in bacteria which would act like peptone in antagonizing sulfanilamide. He obtained from streptococci an extract which did possess this property and was about one hundred times as active as peptone. At about the same time, Fleming<sup>16</sup> was able to show that killed bacteria added to a sulfanilamide-containing culture interfered seriously with the action of the drug. Green<sup>17</sup> obtained an extract from *Brucella abortus* which displayed nonspecific growth-stimulating and sulfonamide-inhibiting properties. Woods<sup>18</sup> made an important advance by tentatively identifying p-aminobenzoic acid as the highly active sulfonamide-inhibiting substance in an extract of yeast. Concentrations of para-aminobenzoic acid of the order of 1:10,000,000 reduced the bacteriostatic effectiveness of 1:10,000 concentrations of sulfanilamide. At the same time Selbie<sup>11</sup> proved that sulfanilamide lost its capacity to protect mice against experimental hemolytic streptococcal infection when p-aminobenzoic acid was administered to the animals along with the drug, thereby establishing, in vivo, the validity of Woods' observations in vitro. Similar confirmation has been reported by McCarty,<sup>19</sup> who finds that para-aminobenzoic acid inhibits the protective action of sulfapyridine on pneumococcal infection in mice. McCarty noted also that p-aminobenzoic acid had no effect on the acute toxicity of sulfapyridine for mice. Similar observations have been reported on human subjects by Strauss and Finland.<sup>20</sup>

The fact that p-aminobenzoic acid is a simple organic compound basically similar to sulfanilamide itself made it possible for Woods to advance an attractive hypothesis of the mode of action of sulfonamides. This hypothesis postulates that p-aminobenzoic acid is an "intermediary metabolite" of essential importance in the process of bacterial cell division. Since p-aminobenzoic acid is not one of the primary growth factors, or substances which must be added to synthetic media in order for bacterial growth to occur, it is assumed that many species of organisms must be able to prepare their own p-aminobenzoic acid from other materials. (Commercial peptone might be a potential source of p-aminobenzoic acid, but attempts to prove this have been unsuccessful.) In order for p-aminobenzoic acid to play its essential role in bacterial metabolism it must be acted upon by a specific enzyme of the cell, and



molecules of sulfanilamide resemble molecules of p-aminobenzoic acid so closely that the two substances compete for position on these enzymes. If all of the positions are gained by molecules of sulfanilamide, which are of no nutritive value to the cell, then the utilization of p-aminobenzoic acid is blocked, and the cell ceases to multiply. Since the affinity of sulfanilamide for position on the enzyme is less than the affinity of p-aminobenzoic acid, complete blockade occurs only when the numerical ratio is strongly weighted in favor of the former; for example, in the case of cultures of hemolytic streptococcus there must be more than a thousand molecules of sulfanilamide for each molecule of p-aminobenzoic acid in order for bacteriostasis to occur. Woods estimates that sulfapyridine is approximately five times as effective as sulfanilamide in competing with p-aminobenzoic acid. Fildes,<sup>21</sup> writing in support of this hypothesis, makes the following statement:

"On this view, the 'sensitivity' of a microbe to sulfanilamide would depend at least in part upon whether it could synthesize p-aminobenzoic acid readily or not. An organism whose synthetic powers were poor would be more sensitive than one with greater power. Similarly, a large number of bacteria would be less affected by a certain concentration of sulfanilamide than a small number. Inhibition or not would become a question of the proportion of sulfanilamide to p-aminobenzoic acid affecting the enzymes of each cell."

Woods<sup>18</sup> explanation is especially attractive because in addition to accounting for variations in the magnitude of bacteriostasis with changes in the drug-bacteria ratio, it offers a basis for interpreting differences in specificity of the various sulfonamides. It is possible that the attachment of pyridine as a prosthetic group to sulfanilamide raises the affinity of the drug for the "p-aminobenzoic acid enzyme"\* in the pneumococcus, and similarly the addition of thiazole increases the specificity for the staphylococcus.

There is no published evidence that the sulfonamide-inhibiting properties of commercial peptone and of tissue digests are due to the fact that they contain p-aminobenzoic acid in some conjugated form. The explanation of the close similarity in properties of these substances awaits further study.

The studies reviewed up to this point have dealt with the effects of sulfanilamide upon bacterial multiplication, and except for the plausible inferences which may be drawn from the work of Woods on p-aminobenzoic acid, there is little which can be used in arriving at a precise chemical definition of the reaction between sulfonamide and bacterium. This review would not be complete without mention of a number of interesting observations which relate sulfonamide action to specific metabolic functions of bacterial cells.

\*This term is employed in only a figurative sense, pending the advancement of more direct proof of the existence of such an enzyme.

**THE PEROXIDE-CATALASE THEORY OF MELLON.**—Mellon,<sup>22</sup> in association with several colleagues, has conducted and published a large number of observations on the action of the sulfonamides as inhibitors of the enzyme catalase. This enzyme is present in abundance in blood cells, exudates, and certain bacteria, and has the property of splitting hydrogen peroxide, liberating molecular oxygen, and therefore preventing the accumulation of peroxide to levels high enough to be toxic to bacteria. Sulfanilamide itself is not strongly antagonistic to catalase, but Mellon believes that certain oxidation products of the drug, including p-hydroxylamino-benzene-sulfonamide, are formed in the body, and he has shown that these substances do tend to inactivate catalase in vitro. According to Mellon's hypothesis, it is the accumulation of peroxide in bacterial cells, brought about by sulfonamide inhibition of catalase, which is responsible for bacteriostasis in vivo. Since hydrogen peroxide is not formed under conditions of strict anaerobiosis, it is a corollary of this theory that the operation of sulfonamide bacteriostasis requires aerobic conditions.

Fox, German, and Janeway<sup>23</sup> and Warren, Street, and Stokinger<sup>24</sup> published experiments which suggested that sulfonamides might poise the Eh of bacterial cultures at a level unfavorable to bacterial multiplication. However, the "poising" effects which they noted were quite possibly the result rather than the cause of bacteriostasis. MacLeod<sup>25</sup> obtained sulfapyridine-susceptible and sulfapyridine-resistant variants of the same strain of pneumococcus, and noted that  $H_2O_2$  accumulated in cultures of the former and not in the latter, thus giving some support to the Mellon hypothesis as it relates to the pneumococcus. MacLeod observed also that the acquisition of sulfapyridine-fastness was associated with a marked loss of dehydrogenase activity for glycerol, lactate, and pyruvate, but not for glucose. Exposure of a sulfapyridine-sensitive strain to the drug caused suppression of the same enzymes.

Fuller and Maxted<sup>26</sup> questioned the validity of the peroxide-catalase theory on the ground that Type 3 strains of hemolytic streptococci, which produce no detectable peroxide in their cultures, are quite susceptible to sulfanilamide. Also, it is difficult to understand how this theory can be reconciled with the known susceptibility to sulfonamides under certain conditions of species as resistant to peroxide as the staphylococcus and the *Bacillus coli*.<sup>27</sup> If there existed some direct evidence (1) that the sulfonamides are active only in oxidized form, (2) that peroxide accumulation on or within bacterial cells actually does occur in spite of the large amount of catalase in body tissues, (3) that bacteriostasis takes place only under aerobic conditions conducive to peroxide accumulation, and (4) that the inhibition of sulfonamide action by p-aminobenzoic acid can be plausibly related to this hypothesis, then it would be possible to accept the peroxide-catalase theory as something more than an interesting and suggestive speculation. In Mellon's most recent paper<sup>28</sup> he has broadened his hypothesis as follows: "In addition to catalase, other enzymes are adversely affected by the

intermediate oxidation products of the sulfonamide compounds. As known so far, they are peroxydase, certain dehydrogenases, and nitratase. The nutrition of the bacteria is thus seriously affected, and bacteriostasis results."

EFFECT OF SULFONAMIDES ON CELL RESPIRATION.—Neither Barron and Jacobs<sup>29</sup> nor Chu and Hastings<sup>30</sup> were able to show any significant effects by low concentrations of sulfanilamide on the oxygen consumption of the heavy saline suspensions of resting bacteria which they employed in the Warburg apparatus. Kempner, Wise and Schlager<sup>31</sup> were able to demonstrate marked suppression of the respiratory activity of growing cultures of *Br. melitensis* by 5 mg. per cent concentrations of most of the chemotherapeutically active sulfonamides. These workers showed, however, that the decreased O<sub>2</sub> consumption was a result of bacteriostasis and failed to note any specific action by sulfanilamide on the respiratory enzymes of *Br. melitensis*. West and Coburn<sup>32</sup> studied the effect of sulfapyridine on the synthesis of cozymase by staphylococcus from nicotinic acid in a basal medium deficient in cozymase. Cozymase contains nicotinic acid. When coupled with protein it forms the dehydrogenases—the enzymes concerned with oxidation or energy transfer in cell metabolism. The staphylococcus requires added nicotinic acid in order to synthesize cozymase but grows well if preformed cozymase is provided. When sulfapyridine and nicotinic acid are both added to the medium, growth does not occur, which suggests that the sulfonamide may compete with nicotinic acid for position in the coenzyme molecule. However, if preformed cozymase is present, sulfapyridine has no bacteriostatic effect in this system. Similarly, Dorfman, Rice, Koser, and Saunders<sup>33</sup> have shown that sulfapyridine inhibits the stimulation of respiration of dysentery bacilli by nicotinamide. These observations are of especial interest for two reasons: (1) they offer support to the general hypothesis that the sulfonamides act as competitive inhibitors of certain essential enzyme systems, and (2) they show that a competitive relationship exists between sulfapyridine and a component of the vitamin B complex of related chemical structure, and known to be essential in the metabolism not only of bacteria, but of animals as well. That reactions of this type may account for some of the deleterious effects of sulfonamides on the host is suggested in a recent report of West,<sup>34</sup> indicating that the administration of sulfapyridine will inhibit the curative action of nicotinic acid (but not of coenzymes) on black tongue in dogs. The specific competition between sulfapyridine and nicotinic acid is probably due to the fact that both agents contain the pyridine nucleus. In spite of the suggestive nature of these studies there is as yet no evidence that the administration to patients of nicotinic acid or thiamin will interfere with the therapeutic action of the sulfonamides.

## INHIBITION OF TOXIN FORMATION

Since many of the toxins or "agressins" of bacteria are probably enzymic in nature, it would not be surprising if the production or activity of certain toxins might be impeded in the presence of sulfonamide.

Levaditi<sup>2</sup> and Carpenter and Barbour<sup>35, 36</sup> apparently succeeded in inactivating the endotoxin of the gonococcus in vitro with sulfanilamide and reported protection of mice with sulfanilamide against otherwise lethal injections of the toxins of staphylococcus, hemolytic streptococci, and *Clostridium welchii*. However, neither Bayliss<sup>37</sup> nor Rigdon and Freeman<sup>38</sup> were able to confirm the work of Carpenter and Barbour on staphylococcal toxins. The general opinion of authors who comment on this subject is that sulfonamides do not directly inactivate preformed exotoxins such as streptococcal hemolysin, but tend to limit their production through bacteriostasis.<sup>39</sup> However, the subject cannot be closed in the face of evidence as suggestive as that of Carpenter and Barbour and of Levaditi, and further work is needed along this line. There would appear to be an open possibility that the sulfonamides may effect unstable combinations with certain toxic bacterial proteins, or endotoxins, and thereby modify their action upon the physiology of the animal.

INFLUENCE OF SULFONAMIDES ON THE PATHOLOGIC SEQUENCE OF  
ACUTE INFECTION

Regardless of the mechanism of the action of sulfonamides on bacterial metabolism, the end result in vivo appears to be the production of bacteriostatic conditions in the zone of infection, and the protection of uninvolved tissues against bacterial invasion. The evidence for this has been reviewed in considerable detail by Long and Bliss.<sup>3a</sup> That host factors are of great importance in complementing sulfonamide effects in vivo has been demonstrated by numerous investigators, particularly Gay.<sup>39</sup> Bacteria which suffer from restricted reproductivity and toxin production are quite naturally more susceptible to ingestion and destruction by tissue phagocytes than bacteria endowed with full parasitic invasiveness.

An interesting description of the influence of sulfonamide on the course of invasive infection has been presented by W. B. Wood, Jr.,<sup>40</sup> based upon serial observations of changes in the pathologic picture of experimental pneumococcal pneumonia in the rat: "During the first 18 hours the drug had little effect upon the advancing pneumonia. The border of the lesion remained irregular and hemorrhagic, and the many pneumococci in the edema-filled alveoli at the margin indicated that the infection was still spreading rapidly.

"At the end of 18 hours there was evidence that the sulfapyridine was beginning to exert its effect. Examination of the pneumococci in the edema zone showed a striking change in their morphology; many

were swollen, pleomorphic, and irregularly stained, and a few had grown in short chains. Forty-two hours after the start of treatment the edema zone had disappeared completely, the pneumococci at the margin having been overtaken by leukocytes. . . . Organisms could still be seen within phagocytic cells after 66 hours of treatment, but by this time macrophages were numerous in the alveolar exudate and appeared to be taking an active part in destroying the bacteria. On the fourth day no pneumococci could be found in the stained sections, and after one week there was extensive resolution with only macrophages remaining in the rapidly clearing alveoli."

There is evidence that the presence of "inhibitor substances" in the zone of infection will restrict the chemotherapeutic effectiveness of sulfonamides just as it limits bacteriostasis *in vitro*. The observations of Selbie<sup>41</sup> and McCarty<sup>42</sup> on *p*-aminobenzoic acid are directly confirmatory of this phenomenon. It has been suggested as a general principle that the resistance to therapy of localized abscesses and necrotizing infections is due in large part to inhibitor substances released by the enzymatic degradation of tissue.<sup>6, 42</sup> MacLeod's<sup>43</sup> discovery of inhibitor substances in a number of organs and exudates, particularly those exposed to enzymic digestion, supplies a sound experimental basis for this supposition. Woods' observation<sup>44</sup> that procaine is an active sulfonamide inhibitor suggests that caution should be employed in administering this anesthetic to patients with active infection who are being treated with sulfonamides.<sup>43</sup> Lockwood<sup>44</sup> has recently prepared a discussion of the application of theoretical considerations regarding the action of sulfonamides to practical problems in surgical therapeutics. It is suggested that the therapeutic result in a given case of established or threatened infection will depend upon the adjustment of three principal variables; namely, the concentration of sulfonamide maintained in the immediate environment of the bacteria, the mobilization of the cellular defense (which of course varies in different tissues), and the concentration of sulfonamide inhibitor substances. In diffuse invasive infections the adjustment of these factors favors effective drug action; in localized or necrotizing infections, sulfonamide therapy will tend to be ineffectual, necessitating surgical intervention. For a particularly interesting discussion along this line the reader is referred to an article by Fleming.<sup>45</sup>

The highly selective action of sulfonamides on bacterial metabolism is evidenced by these two remarkable facts:

1. Concentrations of sulfonamide in the tissues as low as 1 mg. per cent or 1:100,000 will produce demonstrable chemotherapeutic effects.
2. Concentrations up to the saturation level, 200 to 1500 mg. per cent, will produce little, if any, demonstrable local injury to host cells, except perhaps through the action as a foreign body of undissolved

drug. Ehrlich himself could scarcely have foreseen the development of drugs with chemotherapeutic indices as high as these!

Successful chemotherapy in bacterial infections has come about by methods of trial and error, through which we have come to abandon the concept of "therapia sterilisans magna" as the keystone of chemotherapy. We are now provided, instead, with substances which can permeate all of the cells and fluids of the body and render them unsuitable as culture media for many bacterial parasites. Since the sulfonamides are usually not injurious to the host cells, there is no interference with the natural cellular mechanisms of phagocytosis and tissue repair. These are the properties of the sulfonamides which explain and justify their ever-increasing use in surgery.

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# Review of Recent Meetings

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## REPORT OF THE MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

HOWARD MAHORNER, M.D.,\* NEW ORLEANS, LA., AND  
FRANCIS H'DOUBLER, M.D., SPRINGFIELD, MO.

THE annual meeting of the American Association for the Study of Goiter was held in Boston May 12, 13, and 14, 1941. The meeting was opened by F. E. Rogers, of Denver, Colo., the President. There were a number of important papers, and frequently during the session the discussions were interesting and prolonged time, showing extreme variability of opinion regarding debatable points.

The first paper was by J. L. DeGourcy, of Cincinnati, Ohio, on the importance of maintaining a normal basal metabolic rate following thyroidectomy. He felt that the problem of preventing recurrence of toxic goiter began at the time of the operation. He was inclined to remove too much rather than too little of the thyroid tissue. Almost immediately postoperatively he began giving the patient thyroid extract. This was not only to prevent symptoms of myxedema but also to prevent thyroid hypertrophy, which is more apt to occur if the administration of thyroid extract is omitted. The amount of thyroid extract given was  $\frac{1}{2}$  gr. daily for approximately three months. He repeated the basal metabolic rate determination at intervals for several years in order to recheck the possibility of hypertrophy of the gland.

For diffuse nontoxic goiter he advised giving desiccated thyroid in increasing doses. This reduces the size of the thyroid and prevents occurrence of toxic symptoms. He has given thyroid extract to three toxic cases. Improvement followed immediately. He has given as much as 6 gr. of thyroid extract daily to these patients.

In discussing this, Blair Mosser, Kane, Pa., said that at the University Hospital in Philadelphia they had given thyroid extract to several patients with goiter. One death resulted which stopped their clinical experiments.

Emil Goetsch, Brooklyn, N. Y., studied cases at the Long Island College Hospital in order to show the relationship of parenchymatous hypertrophy and hyperplasia of the thyroid gland to Riedel's struma. His thesis was that fully developed Riedel's struma began many years earlier as an actual hyperplasia of the thyroid and that the end stage was diffuse fibrosis. He believed that hyperplasia acted as an irritant and produced local inflammatory changes in the thyroid gland that went on to fibrosis. In support of his theory he studied 22 children under the age of 12 years and showed areas of lymphocytic infiltration in the glands removed from these children. In older patients, he found inflammatory fibrosis associated with the areas of hyperplasia. In the areas that did not have any hyperplasia in the glands, there was no evidence of fibrosis.

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John de J. Pemberton, Rochester, Minn., and Allen Graham, Cleveland, Ohio, dissented from the idea that true Riedel's struma was the ultimate result of hyperplasia in hyperthyroidism.

J. Lerman, Boston, Mass., gave some further observation of this pituitary type of myxedema. Attention to this type of myxedema was aroused by a patient who apparently had myxedema but who on the administration of thyroid extract went into coma. He cited another patient who on several occasions had had coma following respiratory infection. The patient had some evidence of myxedema, but there were atrophic breasts, amenorrhea, and loss of libido, hypochromic anemia, and a very low basal metabolic rate of minus 40 to minus 52. The cholesterol was low, 112 mg. per cent. The administration of thyroid extract in this case resulted in hypoglycemia. Salt elimination resembled Addison's disease. There was a low blood sodium and chloride. The case was in reality a type of panhypopituitarism. In the treatment the indications were for a high salt diet and gonadogen. The administration of pituitary extract did not prove satisfactory. In myxedema of pituitary origin the blood cholesterol is low or normal. The administration of thyroid extract in these instances may produce an adrenocortical failure.

In the discussion J. H. Means, Boston, asserted that the problem was in reality one of "when is myxedema not myxedema?" The answer is: "When it is a kind of 'Simmond's disease.'" He stated that if thyroid extract does not help myxedema, it is probably myxedema of the pituitary type.

D. Henry Poer, of Atlanta, Ga., discussed his experience with the treatment of parathyroid tetany with dihydrotachysterol and vitamin D<sub>2</sub>. Dihydrotachysterol was discovered when hyperirradiated viosterol finally resulted in a product in which vitamin factor is destroyed and the calcium-controlling factor highly increased. It was obvious that it was the very thing necessary for the treatment of tetany. Poer had treated 12 cases of tetany. In certain of these the condition was mild and the oral administration of calcium controlled the symptoms (3 cases). Six patients were treated with calcium and dihydrotachysterol. They remained symptom free under this therapy. Two cases were treated with calcium and vitamin D<sub>2</sub>. They remained symptom free under this therapy. In the acute cases the administration of calcium and vitamin D and parathormone is indicated, but in chronic cases the symptoms can be controlled with dihydrotachysterol or with calcium and vitamin D<sub>2</sub>.

H. B. Friedgood, Boston, discussed experimental exophthalmos and its physiologic and clinical significance. He recalled the work of Shockaert who produced exophthalmos in ducks by repeated injection of anterior pituitary extract and his own subsequent experiments in producing exophthalmos in guinea pigs by the same method. He believes that the exophthalmos factor is different from thyrotropic hormone, because after a period of time the hyperplasia of the thyroid gland resulting from anterior pituitary extract subsides and yet the exophthalmos becomes more pronounced as the injections are continued. Probably the host develops an antibody to the thyrotropic hormone but not to the exophthalmos-producing hormone. The exact cause of the exophthalmos is not explained, but experimentally as well as clinically there is edema of the orbital tissues and muscles.

A. C. Davis, of Rochester, Minn., read a paper on the diagnostic significance of paralysis of the vocal cords in diseases of the thyroid gland. His thesis concerned only cases that had paralysis of one or both vocal cords both before and after operation. In 6,754 cases of adenomatous goiter the incidence of paralysis

before and after operation was 0.4 per cent. In 6,453 cases of exophthalmic goiter the incidence of paralysis was 0.06 per cent. He studied 210 cases of carcinoma of the thyroid of which 163 had sufficient data to include in the report. In 14.7 per cent of these there was a paralysis of the vocal cord both before and after operation. He concluded that finding paralysis of the vocal cord is a distinct aid in the diagnosis of malignancy. However, paralysis is more likely to occur in cases in which the malignancy is a diffused type, when the diagnosis can be made fairly accurately without paralysis. In 57 cases of thyroiditis there was no paralysis of the cord; thus in the instance of a hard gland in which there may be some doubt as to whether the cause is malignancy or inflammation, paralysis of a vocal cord is in favor of malignancy.

In discussing this paper, Richard Cattell, Boston, said that the incidence of postoperative paralysis at the Lahey Clinic had been reduced to one-third of its previous 1 to 3 per cent level by routine exposure of the recurrent laryngeal nerve. John de J. Pemberton reported a case of bilateral cord paralysis observed preoperatively. Removal of the thyroid gland resulted in restitution of function of the nerves.

R. S. Dinsmore, of Cleveland, Ohio, called attention to the familial factor in exophthalmic goiter in children. He studied 124 cases occurring in children and 14, or 11 per cent, showed a definite familial history. It is true that the larger number of exophthalmic goiter cases develop spontaneously, but the fact that a familial history can be elicited in a large number of cases should indicate the possible etiologic significance of this factor. He reported a child whose mother and grandmother both had exophthalmic goiters.

John Pemberton cited his observation of the occurrence of exophthalmic goiter in identical twins.

Willard Bartlett, Jr., of St. Louis, Mo., reported his studies on the acid-base balance in thyroid disease. In a large number of cases he had studied carbon-dioxide combining power of plasma. These determinations were made on admission, in the preoperative stage, and at the time of discharge on patients who had thyroidectomy for Graves' disease. None of the values were outside the normal range, but more toxic patients have a lower initial carbon-dioxide combining power, and after exertion carbon-dioxide volume per cent falls in the hyperthyroid patient but not in the normal individual. In studying patients on constant diets, he found that the total titrable acidity of the urine excreted in twenty-four hours diminished in the preoperative period of preparation from four to seven times; i.e., as the patient improved. There was evidence of acidosis in hyperthyroidism. The acids are ketone acids and his laboratory has found increases of ketone acids in the blood. He believes that fluids are retained in exophthalmic goiter patients. There is a negative fluid balance.

J. K. McGregor, Hamilton, Ontario, discussed thyroid crisis. He had observed recently 2 cases occurring spontaneously in a preoperative stage. Both the patients had very intense hyperthyroid reactions and 1 died eight hours after admission. The other recovered after remaining in coma for ten days. He wrote to different members of the society and asked their opinions regarding the occurrence of preoperative thyroid crisis. He was surprised to find that it was apparently more common in certain areas than others and that it was not uncommon in New Orleans. He defined thyroid crisis as an overwhelming disturbance of heat-regulating center with intensifications of hyperthyroid symptoms. He outlined a treatment including such measures as intravenous administration of dextrose, oxygen

inhalation, iodine in large amounts, ice packs, rectal irrigations. Thyroid extract has been suggested by some. Preventive treatment is more important than the active treatment since by far the larger number of these cases are postoperative. The stage operations are indicated for certain patients. There was a long discussion concerning this subject. The paper was discussed by A. L. Lockwood, Toronto, Willard Bartlett, Jr., St. Louis, G. C. Shivers, Colorado Springs, Colo., Martin Tinker, Ithaca, N. Y., and Howard Mahorner, New Orleans. Willard Bartlett, Jr., indicated that the febrile reaction was not the only aberrant part of this picture. Even if one was able to reduce the temperature to normal by cold baths, patients may go ahead and die irrespective of that. The discussion in general indicated the absence of anything specific with which to combat these cases and the difficulty of handling crisis once it has begun.

D. M. Clute, of Boston, Mass., read a paper on the clinical relationship between iodine feeding and the operability of goiter. In 750 goiter patients 283 had exophthalmic goiter. Forty-seven per cent of these had had iodine before coming for surgery and 53 per cent had had no iodine. He was able to perform one-stage thyroidectomy on only 60 per cent of the patients who had had iodine and on 87 per cent of the patients who had not had iodine before coming for surgery. He indicated that operation was safer after the first administration of iodine and that the administration of iodine promiscuously in the medical treatment of goiter was no favor to the patient.

The second morning of the meeting was taken up with clinical demonstration at the various hospitals in the city. These observers visited the surgeons at the Lahey Clinic, at the New England Deaconess and the New England Baptist Hospitals, seeing there a number of thyroidectomies performed by Frank Lahey, Richard Cattell, and Herbert Adams. These surgeons demonstrated exposure of the recurrent laryngeal nerve which they accomplished with facility and without loss of time. A case of Hashimoto's disease was presented by Richard Cattell.

F. E. Rogers read the presidential address. He reviewed the development and treatment of goiter. In ancient times the Chinese chewed seaweed as a treatment for goiter. The first monograph on goiter was published in 1556 by Thomas Wharton. In 1791 Desault performed a successful thyroidectomy. Coindet, of Geneva, first used iodine for goiter in 1820. Billroth in 1877 reported the injection of iodine directly into the gland. Billroth stated that 29 out of 35 cases were cured by this method. At this time, Billroth had performed thyroidectomy 20 times for goiter. Eight of these patients died of sepsis. In 1880 Sandstrom discovered the parathyroid glands, but their function was not defined until 1891 by Gley. Murray, of England, first used thyroid extract to cure myxedema in 1891. In 1893 Fredrick Mueller discovered increased metabolism or gaseous exchange in hyperthyroidism. The active use of the basal metabolism for diagnosis for thyroidism, however, did not come into general use until about 1917. In 1914 Kendall isolated thyroxin and in 1922 Plumber reported the use of iodine preoperatively and more or less standardized our modern preoperative preparation for thyroidectomy. Numerous other interesting advances were brought out in Roger's paper including some of the more modern ideas of the management of goiter.

V. E. Chesky, Halsted, Kan., discussed the incidence of liver damage in thyroid disease. In 300 consecutive goiter cases at the Hertzler Clinic liver function tests have been done. The hippuric acid test was used and in nontoxic nodular goiter 100 per cent of the cases had a normal liver function; whereas, in the toxic nodular goiter only 67 per cent had normal liver function and 12 per cent had severe liver damage. In diffuse colloid goiter 72 per cent had normal liver

function and 9 per cent had severe liver damage, and in hyperplastic goiter only 43 per cent had normal liver function and in 41 per cent the liver damage was found to be severe. He felt that it was possible to increase liver function pre-operatively. Some of the measures used for the improvement of liver function for the administration of liver concentrate, vitamin B complex, glycine (6 Gm. a day), and dextrose.

A paper by S. Hertz, R. Williams, and J. H. Means, of Boston, on Graves' disease with dissociation of ophthalmopathy and thyrotoxicosis, was read by R. Williams. In twenty years at the Massachusetts General Hospital they found the records of 89 patients with marked exophthalmos, pupilledema, lid retraction, and failure of extraocular movements. In the group of patients they discussed the basal metabolic rate was usually low. Thirty-nine of the patients had not been operated upon. They felt that the result as far as the eye was concerned was worse in the operated group. Their explanation was that the thyroid activity antagonizes the pituitary output of thyrotropic hormone which they believed is a factor in exophthalmos. They think removal of the thyroid gland results in further increase in the output of thyrotropic hormone. They experimented on rats. Thyroidectomy increased the body water from 66 to 70 per cent and the administration of thyrotropic hormone made still further changes in body fluids. They recommended the administration of thyroid extract and the avoidance of operation in such cases if possible.

This paper was discussed by a number of thyroid surgeons of large experience. In general they did not agree that operation should be withheld in these cases. A. L. Lockwood, Toronto, said he believed the best treatment for an exophthalmos due to exophthalmic goiter was early thyroidectomy and that it did not seem advisable to withhold the benefit of thyroidectomy from patients with hyperthyroidism for fear the exophthalmos would get worse.

On Tuesday evening the Association held its annual dinner. E. H. Rogers served as toastmaster. T. C. Davison, Atlanta, Ga., presented a Memorial Gavel to the Association, a gavel made from wood taken from a dogwood tree on the farm of Crawford Long.

Frank Lahey traced the development of thyroid surgery from an unpretentious beginning to its present extensive importance. Reduction in mortality was ascribed to developments in operative technique, handling of complications, and anesthesia. In reviewing over 20,000 cases, Lahey discussed in turn apathetic hyperthyroidism, multiple-stage operations, thyrocardiac cases, and the relation of function of the liver to thyroid disease. He showed a moving picture illustrating the technique of removal of an intrathoracic goiter too large for intact delivery.

The Van Meter Prize was awarded to Asher Chapman, of the Mayo Clinic, for his studies on Relationships of the Thyroid and Pituitary Glands to Iodine Metabolism, and Extra-Thyroidal Iodine Metabolism.

The first honorable mention was given to L. A. Turley, Ph.D., and E. M. Richter, Ph.D., of the University of Oklahoma, for their work on Relation of Lymphocytosis to Hyperthyroid States.

The second honorable mention was awarded to Wm. L. MacKenzie King, of the Mayo Clinic, for his research on So-Called Lateral Aberrant Thyroid Tumors.

Asher Chapman discussed **Relationships of the Thyroid and Pituitary Glands to Iodine Metabolism**. He studied three sets of animals: intact, thyroidectomized, and hypophysectomized. These were further divided into subgroups, on normal and subnormal iodine intake. An increase in the thyrotropic hormone was found in the urine of thyroidectomized animals. Studies were made of the response (weight, acinar appearance, and vascularity) of the thyroids of intact animals to the stimulus of low iodine intake. A similar study was made on the hypophysectomized animals, and it was found that the thyroid gland is able to respond to the stimulus of low iodine intake in the absence of the pituitary gland. The response of hypophysectomized animals is similar in kind and proportion to that in intact animals, though starting from a different level.

T. O. Young, Duluth, Minn., in **Surgical Treatment of Thyrotoxicosis as Related to Geriatrics**, cited statistics showing that (in Duluth) although there is a decrease in thyroidectomies in general, there is an increase in the aged undergoing thyroid surgery and also in the aged receiving medical care for thyrotoxicosis. Apathetic hyperthyroidism is relatively more frequent in the aged. The importance of preoperative preparation and of multiple-stage operations on the aged was stressed. The use of vitamin B (especially B<sub>1</sub>) and of oxygen and moderation in sedation were advocated.

Irvin Abell, Louisville, Ky., Chairman of the Defense Committee of the American Medical Association, was called upon for a few remarks. He discussed the committee's work and recent developments as regards deferring (from draft) medical students and interns, pointing out that the production of doctors must not be bottlenecked.

J. H. Hutton, Chicago, Ill., discussed nouthyroid conditions causing low and high basal metabolic rates. He reported cases of patients with obesity taking thyroid extract without increase in pulse rate and with loss of weight. He also discussed Fröhlich's syndrome and thin patients with low basal rates. Patients with low basal rates without thyroid symptoms are probably not hypothyroid, especially if they do not become better on thyroid medication. One must consider pituitary and adrenal deficiencies in this respect.

J. W. Hendrick, Amarillo, Tex., in **Use and Abuse of Iodine in the Management of Goiter**, reviewed 600 cases, of which 512 had received iodine treatment; the remaining cases had not had iodine therapy and had not been previously diagnosed. Hendrick suggested the use of iodine during pregnancies in endemic regions and in treating nontoxic goiters especially in school children. Results obtained from a questionnaire sent out to members of the Association were given. This dealt with the use of iodine. In mild hyperthyroidism 88 per cent of those answering prefer operation after lugolization. In mild recurrent cases 70 per cent try control with iodine; in treating nontoxic nodular goiter 99 per cent are opposed to the use of iodine. In preparing toxic nodular goiters 79 per cent are in favor of using iodine.

J. de J. Pemberton, Rochester, Minn., read a paper on **Papillary Adenocarcinoma of the Thyroid**. There are two schools of thought as to origin: (1) stimulation of inferior thyroid tissue rests; (2) metastases secondary to carcinoma of the thyroid. Those patients in whom lateral cervical tumor was the main complaint were classed as having aberrant thyroid tissue irrespective of the thyroid gland. The second group comprised cases in which malignancy of the

function and 9 per cent had severe liver damage, and in hyperplastic goiter only 43 per cent had normal liver function and in 41 per cent the liver damage was found to be severe. He felt that it was possible to increase liver function pre-operatively. Some of the measures used for the improvement of liver function for the administration of liver concentrate, vitamin B complex, glycine (6 Gm. a day), and dextrose.

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(0.3 per cent). Studies were given of blood chemistry and liver function before and after the use of sodium pentothal. Electrocardiographic studies during pentothal anesthesia were presented and moving pictures were shown. The conclusions drawn are that sodium pentothal produces a condition most resembling sleep. Oxygen must be given during anesthesia. A large series of cases was reported.

J. H. Vanden Berg, Grand Rapids, Mich., read a paper on **Mild Unrecognized Hypofunction of the Thyroid**. Cases of mild hypothyroidism with so-called normal basal metabolic rates were discussed. These patients have too little physical reserve; they lack "pep" and have little vitality. Mild and unrecognized hypothyroidism is very definite and more distressing than mild unrecognized hyperthyroidism. Too many of us accept the range of minus 10 per cent to plus 10 per cent of the basal metabolic rate as normal. Under thyroid medication the rate may not be raised although the patient improves.

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## MEETING OF THE AMERICAN SURGICAL ASSOCIATION, APRIL 28-30, 1941, WHITE SULPHUR SPRINGS, W. VA.

J. DEWEY BISGARD, M.D., OMAHA, NEB.

**ADDRESS** of the President, David Cheever, Boston.—A scholarly historical review of the influence that wars have had upon the development of the art and science of surgery and of surgeons and the influence that this art and science has had upon the outcome of wars and the fate of civilization, this address, as a classic in content and composition, cannot be reduced to an abstract and must be read in its entirety.

**Intestinal Antisepsis, With Special Reference to Sulfanilylguanidine**, Warfield M. Firor and (by invitation) Edgar J. Poth, Baltimore.—Experiences with this drug in both clinical cases and experimental animals have confirmed previous observations that it is not absorbed as rapidly from the bowel as the other sulfonamides and is more effective in reducing the concentration of coliform organisms in the intestine. The reductions in bacterial flora following its use have not been sufficiently consistent or significant, however, to warrant its use as preoperative measure for intestinal surgery. Some cases, particularly those with ulcerating lesions of the bowel, are entirely refractory to the drug and others show reductions in bacterial counts only after the administration of enormous doses. No severe toxic symptoms have been observed. The use of the drug is contraindicated in the presence of obstruction, ulcerating lesions, and renal damage.

Harvey Stone, Baltimore, reported that he had used the drug in 8 cases of ulcerative colitis with no apparent benefit and observed also in 25 cases preparatory to colonic surgery without significant bacteriologic or clinical benefit to warrant continuing its use in the future.

**Aseptic Immediate Anastomosis Following Resection of Carcinoma of the Colon**, John H. Gibbon, Jr. and (by invitation) Clare C. Hodge, Philadelphia.—A comparative analysis of the mortality in 118 cases of resection of the abdominal colon by the techniques of closed exteriorization, open primary anastomosis, and aseptic primary anastomosis was given. This is a collected series from several surgeons.

thyroid gland was the main complaint and in these the lateral masses were considered as metastatic. In all cases of both groups all the lateral nodes should be completely removed together with the entire thyroid lobe on that side whether or not a tumor is felt in the lateral lobe. Postoperative irradiation should follow. If the carcinoma is of the papillary type, the prognosis is not bad.

**J. B. Kent**, Denver, discussed **One Reason for Failure in the Surgical Control of the Toxic Hyperplastic (Exophthalmic) Goiter**. According to his view post-operative crisis is in proportion to the amount of gland left and is due to the secretion of this gland residue and does not occur after total thyroidectomy. For these reasons he is opposed to multiple-stage operations.

**E. J. Bartels**, Boston, found in studying diarrhea in hyperthyroidism that 92 per cent of cases with hyperthyroidism have exaggerated peristalsis. Possible causes of diarrhea in hyperthyroidism were listed: direct action on musculature, vagal action, reduction of gastric acids, retarded absorption, altered pancreatic secretion, reduced hepatic function, altered adrenal function. Lipocaine is a specific internal secretion of the alpha cells in the pancreas and is distinct from insulin. It has to do with handling of fat. It is active when given either hypodermically or by mouth. Hyperthyroidism has a depleting effect on the alpha cells of the pancreas. Six cases of hyperthyroidism with diarrhea were treated with lipocaine with restitution of bowel function to normal. The treatment is considered as supplementing the secretion of the alpha cells of the pancreas.

**W. O. Thompson**, Chicago, discussed **Persistence and Recurrence of Toxic Goiter Following Subtotal Thyroidectomy**. There are remissions and relapses in cases of recurrent and persistent hyperthyroidism just as in cases of hyperthyroidism before operation, and the size of the tissue likewise changes. If iodine will not hold the recurrent or persistent case within reasonable limits, a second operation should be performed. Psychic trauma and its effects were discussed. Cases operated upon by more experienced surgeons have less postoperative thyrotoxicosis. Sometimes the amount of tissue left seems to have little to do with the problem.

In the discussion, **Allen Graham**, Cleveland, and **V. E. Chesky**, Halsted, Kan., considered the behavior of the remaining lobe after lobectomy in hyperthyroidism.

**Martin B. Tinker**, Ithaca, N. Y., gave a most interesting survey of the history and development of thyroid surgery with which he has been intimately connected. Thyroidectomy for uncomplicated goiter has a negligible death rate, but the multiple-stage operation for hazardous cases is still not used as often as necessary. The advantages of the electric knife were discussed. Tinker advocated wider use of multiple-stage operations. Packing and temporary closure are especially called for in cases of suppurative thyroiditis and extensive malignancy. In cases of extensive malignancy he advocates excision with the electric knife of what can be removed and radiation of the rest.

**C. N. Carraway**, Birmingham, Ala., and **T. C. Davison**, Atlanta, Ga., reported **The Use of Sodium-Pentothal-Oxygen Anesthesia in Thyroid Surgery**. The chemistry of sodium pentothal was discussed and its action on the central nervous system. The medulla is last affected. Rapid action is obtained via the blood stream. Oxygen administration obviated anoxemia. Atropine given preoperatively prevents secretion and laryngeal spasm. Picrotoxin is an antidote



the symptoms persisted were those in which the pylorus had not been removed or in which enteroanastomosis had been performed at the time of partial gastrectomy. The operative mortality during active hemorrhage is no more than 5 per cent if done early but is very high (30 to 100 per cent) if done late when the patient is exsanguinated.

J. V. Bohrer, New York City, presented statistics showing that although hemorrhages are more often fatal in patients over 45 years of age, they not infrequently cause death in the younger individuals. M. M. Zininger, Cincinnati, reported a series of 92 cases with bleeding ulcers in which 10 per cent died of hemorrhage.

**Gastric Ulcer: The Significance of This Diagnosis and Its Relationship to Cancer,** Arthur W. Allen and (by invitation) Claude E. Welch, Boston.—A study has been made of all cases diagnosed as gastric ulcer admitted to the Massachusetts General Hospital during the period 1930-1939. It is shown that cancer of the stomach was present, rather than ulcer, in 12 per cent of all the cases, and in nearly 40 per cent of those cases in which resections were performed and pathologic sections were available. The present method of treatment of gastric ulcer, implying medical observation for a period of time, results in a considerable delay in the diagnosis of many gastric cancers and overlooks a definite hazard of medical therapy. Subtotal gastrectomy can now be performed for gastric ulcer with a reasonable mortality (6.4 per cent in the past five years). This produces almost uniformly excellent results if the lesion is found to be a benign ulcer, a comparatively high percentage of cures if cancer is present. It is therefore proposed that gastric ulcer be considered fundamentally a disease demanding surgical therapy and that a short period of medical treatment be condoned only if the ulceration is acute, inaccessible, or in a poor-risk patient. Gastrosopic examinations in these cases did not prove to be more accurate than x-ray studies in differentiating ulcer and carcinoma.

Frank Lahey, Boston, pointed out that at the Lahey Clinic only 7 per cent of duodenal ulcers are treated surgically; whereas, 27 per cent of gastric ulcers are operated upon. J. S. Horsley, Richmond, Va., stated that partial gastric resection is indicated in most cases of gastric ulcer. Fordyce B. St. John, New York City, stated that most statistical reports of permanent cures of ulcers are relatively premature because ulcers do recur after a quiescent period of as long as ten years or more. R. Graham, Toronto, reported a diagnostic error of 9 per cent in question of ulcer and carcinoma of the stomach in his series of cases. He also reported an operative mortality of 35 per cent in cases operated upon during a massive hemorrhage.

**Skin Grafting and the "Three-Quarter-Thickness" Skin Graft for Prevention and Correction of Cicatricial Formation,** Earl C. Padgett, Kansas City, Mo.—The technique of using the author's dermatome and the advantages offered by it were well demonstrated. With it a large sheet of skin of any desired thickness and of constant thickness can be cut rapidly not only from the thighs and abdomen but from such surfaces as the thoracic wall. The three-quarter-inch-thickness graft is the most ideal for most purposes. It is thick enough to give an excellent cosmetic and functional result and contains sufficient derma to minimize contractures. It is more likely to survive transplantation than a full-thickness graft. He reported a survival record of 96 per cent.

Robert H. Ivy, Philadelphia, warned of the need of experience in the use of the dermatome. V. Blair, St. Louis, stated that grafts cut with the dermatome

The mortality with aseptic anastomosis (Kerr technique) was 13 per cent, that with the other 2 techniques, 28 per cent. Resection should not be done in the presence of obstruction. The obstruction should be relieved by cecostomy before resection is undertaken.

Wm. B. Parsons, New York City, emphasized the importance of the Miller-Abbott for both pre- and postoperative decompression in these cases, often eliminating the necessity of cecostomy. The use of the tube in his series of cases had resulted in a reduction of mortality from 22 to 6.7 per cent. Harry B. Kerr, Washington, D. C., reported 107 resections with a mortality of 15 per cent in 39 performed by the aseptic technique as contrasted to 35 per cent in 68 performed by the other techniques. Richard B. Cattell, Boston, reported 275 resections carried out at the Lahey Clinic by the closed exteriorization technique with a mortality of 13 per cent. Leo Eloesser, San Francisco, described a method of anastomosis by telescoping or invaginating the end of one loop into the other. He believes this gives greater assurance against leakage.

**Surgical Management of Carcinoma of the Ampulla of Vater and Distal End of the Common Duct,** Verne C. Hunt, Los Angeles.—Ampullary and periaampullary carcinomas are usually of relatively low grade malignancy and often are resectable. Diagnosis is suggested by persistence of occult blood in the stool in presence of painless jaundice.

Four (personal) operated cases were reported, 2 of transduodenal resection with reimplantation of the ducts and 2 of the one-stage Whipple operation; 3 survived with good operative results. Operation has been made much safer by control of the hemorrhagic tendency of these jaundice cases with vitamin K. Pancreatic fistula has been a dangerous, troublesome, and rather constant complication of the Whipple operation. It did not occur in Hunt's last case in which the technique was modified by cupping the resected end of the pancreas with the open end of duodenum left after resection of its proximal portion.

Allen O. Whipple, New York City, discussed the advantages of the one-stage operation and reported 1 case successfully resected in one stage. Thomas Orr, Kansas City, Mo., reported 2 cases successfully resected by the Whipple technique, one in two stages and one in one stage. Both had pancreatic fistulas which closed; both are well. Dallas B. Phemister, Chicago, reported 3 cases and demonstrated that it is possible in some cases to demonstrate the presence of a tumor by special and careful x-ray studies. Morris K. Smith, New York City, emphasized the difficulty in palpating the tumor at operation and reported 1 case in which gall bladder drainage was established at the first operation and tumor found upon reoperation for persistence of obstruction.

**Results of Partial Gastrectomy for Bleeding Duodenal, Gastric and Gastrojejunal Ulcers,** Waltman Walters and (by invitation) William H. Cleveland, Rochester, Minn.—Of 122 patients on whom partial gastrectomy was performed at the Mayo Clinic for bleeding duodenal, gastric, or gastrojejunal ulcers, the follow-up study disclosed that partial gastrectomy for bleeding ulcers of the stomach and duodenum was followed by excellent results in from 90 to 91 per cent of cases; hemorrhages and symptoms of ulcer did not recur. This was true, however, in only 80 per cent of cases in which operation was performed for bleeding gastrojejunal ulcer. Of 100 patients traced, only 1 died after gastrectomy from hemorrhage. In the group of cases in which hemorrhage occurred after gastrectomy, there was usually but a single episode which was not serious. Occasionally the hemorrhage was associated with an ulcer type of pain. Most of the cases in which

it is removable. As certain benign tumors are potentially malignant and as many malignant tumors may be removed completely, practically every case of intrathoracic tumor should be promptly explored surgically if there is no evidence of metastasis or hopeless invasion of the adjacent thoracic walls. Preoperative pneumothorax is rarely informative except in distinguishing between pulmonary and mediastinal or thoracic wall tumors. Tumors that might be lymphoblastomatous should be given a diagnostic test dose of deep x-ray therapy. The difficulty of differentiation between the expansile pulsation of a mediastinal aneurysm and the transmitted pulsation of a true neoplasm was emphasized.

S. W. Harrington, Rochester, Minn., emphasized the importance of lateral and oblique roentgenograms in diagnosis. Two cases of substernal diaphragmatic herniation were reported showing difficulty in their diagnostic recognition.

**Endometriosis: Its Significance,** Joe V. Meigs, Boston—In 363 consecutive abdominal gynecologic operations, gross or microscopic evidence of endometriosis was found in 25 per cent of cases. It is much more commonly encountered in private patients than in those of charity clinics. Late marriages and late conception may be etiologic factors.

James C. Masson, Rochester, Minn., stated that he had not observed any evidence of social sexual relationship to the occurrence of endometriosis.

**Symposium of Surgical Preparedness: Emergency Treatment of War Injuries of the Face and Jaws,** Robert H. Ivy, Philadelphia—A correlated plan of treatment from the advanced zone to the installations in the rear shortens the average period of disability of this type of injury and increases the number ultimately restored to approximately normal function and appearance. Control of hemorrhage and treatment of shock are the most urgent early considerations. Establishment of adequate air passage demands special measures. In fractures of the jaws, any bone fragments still attached to soft tissues should be carefully preserved. Carelessness in early cleansing of wounds and removal of shattered fragments frequently results in loss of important segments, malunion, nonunion, and secondary deformity. Temporary fixation of bone fragments should precede closure of soft tissues where possible. In fixation of jaw fractures collaboration of surgeon and dental officer is essential. In transportation from the combat zone, cases of oral and pharyngeal wounds preferably should sit up. If he must be recumbent, the patient should be placed face down if there is danger of obstruction in the air passages.

Lieut. Col Roy A. Stout, Dental Corps, U. S. Army—Fractures of the jaw are treated by wiring of teeth when available, otherwise by traction applied through a fixed point in front of the face or by internal fixation. A fixed point for applying traction can be established with a tongue depressor fixed to the forehead and along the bridge of the nose or a wire tripod in front of the face fixed to a plaster headgear. V. Blair, St. Louis, stated that bad cosmetic results are usually attributable to poor initial treatment rather than to actual destruction. James B. Brown, St. Louis—Often fragments can be fixed with Kirshner wires. Loose fragments should always be preserved and used in restoration.

**Organization for Evacuation and Treatment of War Casualties,** N. T. Kirk, Colonel, M. C., U. S. Army (by invitation).—The general plan of organization for the emergency treatment and evacuation of the injured from front lines to the base hospitals was presented.

take better because the cut surface is smooth and even and in the cutting the skin suffers less trauma.

**Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in the Treatment of Hypertension, Keith S. Grimson** by invitation of Dallas B. Phemister, Chicago.—There are two types of experimental essential hypertension, a neurogenic type and a type produced by renal ischemia. Experimental studies related to the role of the sympathetic nervous system in part and as a whole in blood pressure regulation and in experimental neurogenic hypertension have suggested that more might be accomplished by total paravertebral sympathectomy than by splanchnic section alone. Complete removal by a two-stage transpleural operation of the thoracic and lumbar paravertebral sympathetic chains, the splanchnic nerves, and the celiac and first lumbar ganglia has been performed on 8 patients with essential hypertension. In 2 other cases the operation consisted in complete bilateral thoracic sympathectomy, removal of the splanchnic nerves, and celiac and first lumbar ganglionectomy. Lowering of the blood pressure has been observed in all instances varying from complete restoration of the blood pressure to normal to only moderate lowering.

**R. H. Smithwick**, Boston, stated that he had approached the problem by carrying out resection in stages until the desired result had been obtained. In 9.1 per cent of cases a good result was obtained by the Peet operation and in these cases no further resection was done. In the remaining cases the lumbar ganglia and trunks and celiac ganglia were resected with good results in 65 per cent. In the cases in which these two procedures failed to give the desired result the upper dorsal ganglia were resected. **George Curtis**, Columbus, Ohio, stated that splanchnic section for hypertension has demonstrated the presence of sensory fibers in the splanchnic nerves. The motor influence of splanchnic section upon the motor activity of the stomach was demonstrated in tracings of peristalsis. **Loyal Davis**, Chicago, stated that sulfocyanate was more effective in reducing blood pressure after sympathetico-splanchnic section even in cases in which the operation fails to lower the blood pressure significantly. **M. M. Peet**, Ann Arbor, Mich., noted that a review of 700 operated cases has shown not only symptomatic improvement in most cases but a definite prolongation of life as judged by the Wagner-Keith mortality table.

**Intracranial Aneurysms: Diagnosis and Surgical Treatment, Walter E. Dandy**, Baltimore.—One-half of the intracranial aneurysms arise from the circle of Willis and are not accessible or amenable to operative treatment. Congenital aneurysms of the intracranial carotid which can be treated surgically are of two types: (a) those in the canal are treated by ligating the artery in the neck and then clipping the neck of the aneurysmal sac or the artery itself within the cranium; (b) those of the intracranial trunk are exposed and either the neck of the sac is ligated or the sac trapped between ligatures. Reported were 13 operated cases of which 10 were cured. The symptoms are third nerve palsy and pain in the eye of the affected side.

**Francis C. Grant**, Philadelphia, pointed out that thorotrast is useful in locating and identifying these aneurysms in suspected but doubtful cases.

**Observations on Intrathoracic Neoplasms, John Alexander**, Ann Arbor, Mich.—Accurate preoperative diagnosis of intrathoracic neoplasms, apart from esophageal carcinomas and those bronchogenic carcinomas that can be biopsied endoscopically, is virtually impossible. In many instances the surgeon cannot tell before operation if a tumor is benign or malignant and if it should be malignant, whether or not

N. T. Kirk, M. C. U. S. Army, expressed a more favorable opinion of the "below-the-knee" amputations. L. Eloesser, San Francisco, stated that with proper construction of the artificial limb "below-the-knee" stumps could be made partially end-bearing and very satisfactory.

**B.I.P.P. and Liquid Paraffin Treatment of War and Civilian Wounds, Fraser B. Gurd and (by invitation) L. H. McKim, Montreal.**—In 1915 Rutherford Morison introduced B.I.P.P. packs for dressing wounds. This paste containing bismuth and iodoform in liquid petrolatum is applied to either fresh or infected granulating wounds. In fresh wounds it is applied to the surfaces after the wound has been débrided and the surfaces dehydrated with alcohol. The wounds are left open, dressed infrequently, and immobilized. The surfaces rapidly become covered with clean healthy granulations permitting early secondary closure. Histologic studies of granulations showed *minimal edema and very few leucocytes*. Bismuth and iodoform poisoning can be prevented by the judicious use of B.I.P.P. A warning of impending bismuth poisoning is manifested by a "lead line" of the gums.

**Present-Day Treatment of Compound Fractures, Robert H. Kennedy, New York City.**—The problems in the treatment of compound fractures were discussed generally. Shock and hemorrhage are the urgent and first problems to be met, then the wounds should be cleaned and débrided and the fractures reduced. Kennedy believes the wounds should be left open to close by granulations or by secondary suture. Reduction in most of his cases is accomplished and maintained by traction. The sulfonamides have been administered routinely as has tetanus and gas antitoxin. There is an increasing need for more training of medical students and young surgeons in the accepted methods of treating fractures.

**Kellogg Speed, Chicago,** stressed the need of more undergraduate and postgraduate instruction in the care of wounds and fractures. During the present war the civilian casualties have exceeded those of combat. Both for the purposes of instruction and military use the types of splints and other armamentarium should be standardized. Wm. Darrach, New York City, believes that the fractures should be reduced at the time the wounds are cleansed. J. A. Key, St. Louis, believes that it is safe and desirable to do a primary closure of most compounded wounds if cleansed, débrided, and sulfonamized within a few hours after injury. J. Dewey Bisgard, Omaha, Neb., presented experimental evidence that the much used chemical bacteriocidal agents usually fail to destroy all bacteria in wounds and seriously injure tissue cells thereby crippling the normal local defense against the bacteria which remain viable in the wounds. Débridement and copious saline irrigations rid the wound of most microorganisms and leave the tissues uninjured to cope with those that remain in the wound. Sulfanilamide causes little or no injury to tissues.

**The Treatment of Compound Fractures Resulting From Enemy Action, Philip D. Wilson (by invitation), New York City.**—The Orr method of treatment of wounds has been adopted by the British Military Surgeons because it has given superior results in respect to both mortality and morbidity, while casting and infrequent dressings have added to the comfort of the patients and simplified transportation and nursing care. Nonpadded casts have been used extensively, splitting the cast immediately through its entire length to allow for swelling. There have been comparatively few anaerobic infections. Air raid casualties have been 10 wounded to 7 killed and there has been much associated shock. The application

**The Cooperation Between the Army Services of Evacuation and Hospitalization, Henry H. M. Lyle, New York City**—Active intelligent cooperation predicates a basic knowledge of the objects desired, the mechanism by which they are to be accomplished, and the character of the personnel. The speed of attack, and the greater use of automatic weapons, has increased the difficulties of the medical department. The technique of triage, surgical management, and evacuation will have to be adapted to the tactics of mechanization and movement, but the principles remain unchanged. In the last war, military operations assumed the traditional fan shaped pattern, today it is a war of depth. An open slashing attack has to be met with an equally mobile defense. Aeroplane transportation of the wounded has possibilities, but motor transportation remains the mainstay. The basic principle of military surgery is debridement, chemotherapy is an adjunct. Immobilization in plaster should be of value in transporting the wounded. The consultants should be more active with the service of evacuation and hospitalization.

**The Role of the Medical Department in Naval Warfare, F. R. Hook, Commander, M. C, U. S. Navy (by invitation)**—The nature of the navy imposes greater individual responsibility upon members of its medical corps. A medical officer may have sole responsibility for the ship's complement. Burns and drowning are frequently encountered in addition to the ordinary injuries. He stated the navy wishes to have available a large medical reserve corps for research and teaching and emergency needs.

**Wm. Darrach, New York City**, pointed out that in war the lightly wounded are of first importance and should receive preference in care and evacuation. **Elliott Cutler, Boston**, stated that no country in the world has available such a wealth of medical and surgical talent. "Give us the tools and necessary equipment and we will furnish the personnel." During the last war there were distressing gross deficiencies in such essential equipment as laundries.

**Leonard R. Broster, M A, M D, M Ch (Oxford), FRCS (England) (by invitation), London, England**—Experience in Spain and in the war to date has established the Winnet Orr method of treatment of wounds as the method of choice for war injuries. It has given uniformly better results in respect to both mortality and morbidity. The wounds are left open and insufflated with sulfanilamide powder. The sulfonamides are administered by mouth. The local treatment of burns has consisted of washing the involved areas with salt solution, drying them, and then applying sulfanilamide powder and an eschar with tannic acid or covering the areas with glycerin especially about the face. As a result of bombing two new types of injuries are frequently observed, the blast injuries and the crush syndrome. The former is characterized by hemorrhage from the lungs which present torn alveoli and grooved impression of the ribs on the surfaces. The latter is characterized by severe shock and by hemorrhages into various organs, particularly the adrenals.

**The Experience of the Canadian Army With Amputations of the Lower Extremity, W. E. Gallie, Toronto**—Through the Department of Pensions and National Health it has been possible to keep an accurate record and to make frequent examinations of all Canadian Veterans of the last war who have amputation stumps. These observations have shown that for working men and bearing stumps, the Syme and Gritti Stokes, are infinitely more useful than other types. Amputations between the ankle and knee should leave a stump not longer than six inches and the fibula should be cut shorter than the tibia. Flaps that are too long and loose and neuromas have been the most frequent causes of trouble.

ing with the recipients' blood. Plasma is as effective as whole blood in the treatment of hemorrhage and hemophilia. It is more effective than vitamin K in the immediate control of hemorrhage in hemorrhagic disease of the newborn.

**The Role of Adrenal Cortical Hormone in the Treatment of Patients With Severe Burns,** Walter Estell Lee and (by invitation) Jonathan E. Rhoads and William A. Wolff, Ph.D., Philadelphia.—Consecutive determinations of the hematocrit and plasma protein concentration in patients with extensive superficial burns make it possible to estimate the probable loss of protein from the circulating plasma and to evaluate the ability of the vascular tree to retain added plasma at various times following the injury. The observations obtained indicate that the abnormal capillary permeability lasts about forty hours. During this period attempts to restore the volume of the circulating plasma to normal result in a temporary increase in the rate of plasma loss from the circulation.

The administration of adrenal cortical hormone enabled the capillary bed to retain substantial amounts of transfused plasma protein twelve to eighteen hours earlier in a majority of instances. Chloride retention in the patients thus treated was so marked that the administration of physiologic saline solution in amounts usually regarded as conservative became hazardous. The combination of adrenal cortical hormone with frequent or continuous infusions of plasma under rigid laboratory control has made it possible to carry patients with as much as 65 per cent of the body surface burned through the period of fluid shift. Evidence has been obtained that the extravasated plasma protein returns to the circulations by the fourth day after the burn. Laboratory evidence of liver and renal injury was obtainable at about this same period even in patients with relatively mild burns.

The cortical extract, estrogen, has been given in doses of 5 c.c. to 6 c.c. per kilogram of body weight every three or four hours. Plasma shift is seldom reversed without treatment in less than seventy-two hours. With adequate plasma transfusions the plasma volume can be returned to normal in one-half the time and the return can be accelerated to one-third or one-fourth with the additional administration of cortical adrenal hormone. The author's formula for calculation of plasma needs in hypoproteinemic patients was presented.

Alfred Blalock, Nashville, reported that animals in shock showed less fall in blood pressure and survived longer when exposed to ordinary room temperature than when they were subjected to higher temperatures.

**The Prevention of Complications Following Radial Head Fractures With Injury to the Anterior Capsule,** Clay Ray Murray and (by invitation) Harrison L. McLaughlin, New York City.—Fractures of the radial head are commonly divided into two groups, those showing separation of the fractured fragments and requiring operation, and those without separation of the fragments requiring only conservative measures. There is a third group of cases, frequently associated with posterior dislocations of the elbow, in which the radial head fragments are displaced anteriorly and in which there are clinical signs of severe damage to the structures of the front of the elbow joint. It is this group to which particular attention is called because of the extreme frequency of extensive ossification in the anterior elbow joint structures productive of prolonged and severe disability. This ossifying process, which involves the anterior capsule and the overlying brachialis anticus, may be markedly increased by the ordinary surgery used for radial head fractures.

In a series of 395 cases myositis ossificans developed in 4.7 per cent. In the 18 cases the operation was done days or weeks after injury and in 12 the radial heads were removed through posterior incisions.

of the Roger Anderson cast-pin-skeletal fixation of fractures of femoral shafts was demonstrated.

**The Effects of Roentgen Therapy Upon Gas Gangrene: Clinical and Experimental Observations, Guy A. Caldwell** (by invitation), New Orleans.—In guinea pigs x-ray therapy has little or no effect in either preventing or altering the course of induced *Clostridium welchii* infections. The excellent clinical results of this therapy as reported in the literature are open to question because in the majority of the reported cases the diagnosis was not established bacteriologically. Furthermore, some recent reports have failed to confirm the earlier ones. It would seem desirable and necessary to discourage the use of x-ray therapy to the exclusion of other established methods until more conclusive evidence of its merit had been demonstrated.

**Frank Meleney, New York City**, stated that the Committee on Surgical Infections of the National Research Council had made a thorough investigation of reported data and was in the process of carrying out further studies. The investigation thus far has shown that x-ray therapy does have a definitely beneficial effect upon the course of *Clostridium welchii* infections.

**The Treatment of Shock From the Physiologic Point of View, C. H. Best** (by invitation) and **D. Y. Solandt** (by invitation), Toronto.—The etiology of shock and therefore its therapy has not been completely solved. Hemoeconcentration with a reduction of circulating blood volume are the physiologic results of plasma loss into extracellular spaces and body cavities plus, in some instances, blood loss. Although the correction of hypoproteinemia and the restoration of normal blood volume by the administration of blood plasma usually restores normal physiologic relations, it is not a complete solution of the problem. Cortical extracts of the suprarenal gland seem to have influence upon the permeability of the capillaries and there is evidence that this extract aids in the treatment of shock and when given preoperatively or before shock is induced experimentally, lessens the degree of shock and delays its onset. It is possible that neurogenic factors, anoxia histamine and other histotoxins, potassium and other toxic substances play a part in the production of shock. Serum is as satisfactory as plasma for use in treatment. The method of lyophilizing plasma was demonstrated.

**Norman E. Freeman, Philadelphia**, presented experimental data showing large losses of plasma into the gastrointestinal tract after trauma and a reversal of the loss following administration of adrenal cortical extract. **Roy McClure, Detroit**, described the simple inexpensive method of drying plasma used at the Henry Ford Hospital. The method was reported in *Surgery, Gynecology, and Obstetrics* in 1910.

**The Clinical Value of Preserved Blood Plasma, Earle B. Mahoney**, by invitation of **John J. Morton, Rochester, N. Y.**—Four hundred injections of pooled lyophilized plasma have been given intravenously without regard to the type of the recipients' blood. The incidence of reactions to the blood plasma has been less than 2 per cent and none of the reactions have been severe. The rediluted plasma has been used in combating shock resulting from trauma, hemorrhage, and burns with apparent beneficial effects on the circulating blood volume. It has been of value in treating the hypoproteinemia resulting from prolonged anorexia, infection, and liver disease. It has been especially valuable in maintaining the fluid balance in the operative and postoperative patients. The advantages of the use of plasma lie in its immediate availability for emergency use, the safety and simplicity of storage, and the freedom from the necessity of typing and cross-match-



(2) lack of operative mortality. The presence of an inflammatory reaction is indicative of a favorable prognosis, and absence of pulsations in the distal arteries is no contraindication to the use of the method. The formula of this zinc chloride paste and a description of the technique of its application appeared in the February, 1941, *Archives of Surgery*.

**Minor Causalgia Following Injuries and Wounds, John Homans, Boston.**—This peculiar state is characterized by hyperesthesia to pinprick and scratch and is often associated with edema and cyanosis. It arises unpredictably from minor injuries such as bruises, fractures, punctured wounds and bites, especially when infected. It may also follow thrombophlebitis. A whole limb, a finger, or a part of the hand may be affected, especially the anatomical part served by a particular nerve such as the median, ulnar, or radial. The disorder is apparently a vicious sympathetic reflex traveling centrally along the nerves serving the blood vessels and reaching the sympathetic by way of a segment of spinal cord. The diagnosis is confirmed by the temporary relief secured by local injections of procaine or sympathetic block. The treatment of this disorder consists in breaking up the vicious reflex by local injections of procaine into a "trigger point," by removing sensitive scars, and by periarterial or paravertebral sympathectomy.

Edwin P. Lehman, Charlottesville, Va., cited cases cured by local excision of scar and of foreign bodies. James White, Boston, recommended that before radical surgery is undertaken the response to novocain block should be ascertained. By early conservative treatment radical procedures may be avoided.

**Mediastinal Parathyroid Tumors. Experience With 15 Out of 54 Cases of Hyperparathyroidism, Oliver Cope by invitation of Edward D. Churchill, Boston.**—Fifty-three cases of hyperparathyroidism have been proved by operation at the Massachusetts General Hospital. Another was explored unsuccessfully; the tumor was found at autopsy lying in the anterior mediastinum in front of the right auricle. Of these 54 cases, adenomas were found in the anterior mediastinum in 10, in the posterior mediastinum in 5. Eight cases had been explored unsuccessfully before coming to this hospital; the adenomas were found in the neck in only 2, in the posterior mediastinum in 1, in the anterior mediastinum in 5. The uncovering of parathyroids in the mediastinum, therefore, presents a major problem. Blind search in the anterior mediastinum is often unsuccessful since a small tumor may not be felt and tumors have been found below the reach of fingers. Parathyroid exploration is now, therefore, divided into two stages: first, the neck and posterior mediastinum are explored, second, the mediastinum is exposed to direct vision by splitting the sternum.

In the presence of an adenoma the uninvolved parathyroid glandules are pale and atrophic, appearing much like fat.

Frank H. Lahey, Boston, noted that a knowledge of the normal and abnormal locations and appearances of these glands is necessary for carrying out a systematic search for a tumor. Occasionally the tumor is found within the substance of the thyroid gland.

**Chronic Ulcerative Colitis: A Summary of Evidence Implicating *B. Necrophorum* as an Etiologic Agent, Lester R. Dragstedt and (by invitation) G. M. Dack and J. B. Kirsner, Chicago.**—The bacterial flora of the colon was studied in patients with ulcerative colitis both before and after deviation of the fecal stream. Flora at first was found to be predominantly aerobic; after deviation it became almost exclusively anaerobic, and one organism, *B. necrophorum*, predominated.

This complication can be much reduced by excising the head through an anterior incision, cauterizing the tissue after the head has been removed, and leaving the fascia open. The operation should be done as soon as possible after injury.

Kellogg Speed, Chicago, stated that early motion was conducive of myositis ossificans and advised immobilization for three weeks following excision of the radial head. The use of a vitallium cap over the end of the radial shaft was demonstrated.

Dr. Murray in closing stated that aspiration of blood and serum from the site of fracture or operation shortened the period of disability.

**Procaine Injection and Early Mobilization in the Treatment of Non-Weight-Bearing Fractures**, L. Kraeer Ferguson, and (by invitation) William H. Erb, Philadelphia.—Leriche, in 1928, first proposed the theory that in sprains and fractures about joints, persistent pain occurs in response to afferent segmental impulses which produce an efferent sympathetic response. This vasomotor stimulation produces vascular or physicochemical changes in the injured area that, in turn, act as a stimulus of continued pain and produce edema and functional disability. By blocking the reflex arc with procaine solution, by injection either at the site of fracture or of the sympathetic ganglia, there is a rapid relief of pain and a disappearance of muscle spasms and joint disability. This permits early resumption of function. This form of therapy, although apparently contrary to all previous teachings regarding treatment of traumatic injuries, has proved by experience to be most effective in the treatment of certain types of non-weight-bearing fractures.

Five to 10 c.c. of 1 or 2 per cent novocain are infiltrated throughout the area of acute tenderness and normal function without splinting or support is carried on. The method is restricted to fractures in which reduction is not necessary and in which weight-bearing plays no part.

Clay Ray Murray, New York City, stressed the merits of the method and the dangers from stretching the limits of its applicability.

**Vascular Injuries**, J. M. Mason, Birmingham, Ala.—In a general review of surgery of the cardiovascular system the influence of recent contributions upon civil and military surgery was stressed. The use of novocain and alcohol block of the sympathetic innervation of the extremities, the employment of heparin, and the increasing availability of whole and dried plasma have greatly altered and extended the usefulness of surgery of the blood vessels.

**The Conservative Amputation of Gangrenous Parts by Chemosurgery**, E. R. Schmidt and (by invitation) F. E. Mohs, and E. L. Sevringhaus, Madison, Wis.—Chemosurgical amputation of gangrenous toes and parts of feet involves chemical fixation of the affected tissue by zinc chloride prior to amputation. After a gangrene-free level is reached, a thin layer of fixed tissue remains for a week or two. On separation it leaves well-vascularized, germ-resistant granulations. Bones and tendons are removed a week or so later. Epithelization is rapid. Scars are smooth and pliable. Of 55 gangrenous lesions involving the feet of 51 patients, healing occurred in 60 per cent after conservative chemical amputation, in 66.6 per cent of 45 cases of diabetic, and in 25 per cent of 8 cases of senile arteriosclerotic gangrene. Lack of healing was usually due to failure of the final layer of fixed tissue to separate. If the basal layer fails to begin to separate within ten days after chemosurgical amputation, the chances for healing are poor, but the patient is still in as good or better condition than before for surgical amputation at a higher level. In this series of conservative amputations chemosurgery was observed to have the following advantages: (1) preservation of a usable foot in a majority of cases and

and sometimes a definite or indefinite abdominal mass. These attacks may subside at this stage and may recur or there may be progression of hemorrhage with collapse and alarming shock. Recovery is usually accomplished with complete rest and conservative treatment, but only once has the diagnosis been made preoperatively. Mindful of the syndrome it should be possible to make the diagnosis from signs and symptoms more often. At operation bleeding vessels have been identified and ligated.

Dallas B. Phemister, Chicago, stated that hemorrhage into the mesentery not infrequently occurs in association with acute pancreatitis.

**The Relationship of Lesions of the Cystic Duct to the Pathogenesis of Cholecystitis.** W. H. Cole and (by invitation) E. O. Hughes and M. V. Novak, Chicago.—Often chronic partial obstruction of the cystic duct can be demonstrated in the gall bladders of patients with cholecystitis.

Partial obstruction at the cystic duct was produced by one of two methods: (1) cutting a flap at the neck of the gall bladder, allowing it to protrude into the lumen at the junction of the cystic duct and the gall bladder; and (2) inversion of the wall at the neck of the gall bladder by "tuck" stitches. In over three-fourths of the cases, definite thickening of the entire gall bladder wall, simulating cholecystitis in human beings, was obtained, but only after the lapse of several months' time. Cultures of the walls of these gall bladders were positive in practically all instances. Control animals in which similar procedures were performed in the dome of the gall bladder were negative for evidence of thickened wall, etc., except at the local point of operative trauma. The experiments do not contradict other mechanisms of producing cholecystitis such as lymphatic spread, etc., in the pathogenesis of cholecystitis, but in reality are supplementary, supposedly representing the initial lesion which might bring about the infection.

Dallas B. Phemister, Chicago, raised the question of priority: May not cholecystitis as seen in man develop first and extend to the cystic duct producing the narrowing and other changes found in these ducts? Mucocoeles have been found in which there were no stones and no obstruction of the cystic duct. Nathan Womack, St. Louis, referred to his experimental studies in dogs showing that aspirated gall bladder bile merely concentrated to one-half its normal volume and then reinjected into the gall bladder caused the changes characteristic of cholecystitis to develop both with and without demonstrable evidence of infection. It is possible that partial obstruction of the cystic duct produces cholecystitis because the obstruction may result in abnormal concentration of the gall bladder bile.

**A Useful Method of Anastomosis of the Gall Bladder or Bile Ducts to the Gastrointestinal Tract.** Vernon C. David and (by invitation) Roy E. Brackin, Chicago.—A technique was presented for anastomosis between the biliary and gastrointestinal tracts. Dogs autopsied as long as one year after anastomosis showed no contracture of the anastomotic opening, no dilatation of the ducts, and no evidence of liver damage. The technique has been used with success in a difficult case of biliary tract disease.

The principle of the technique consists of placement of strangulating sutures between the approximated walls of the gall bladder or bile duct and the stomach or bowel. Following necrosis of the strangulated tissue an anastomosis is established.

This organism has been found in the diseased colon in a great majority of patients examined and isolated in pure culture in a mesenteric lymph gland and a portal thrombus. Specific antibodies have been found in the blood of ulcerative colitis patients, but not in the blood of normal individuals. A number of different strains of *B. necrophorum* have been isolated and antibodies to the specific strain found in the colon have been present in greater concentration in the patient from whom the strain was isolated than in other patients with the disease. *B. necrophorum* has been found to be more plentiful in the isolated colon during periods of exacerbation of the disease and less numerous during periods of quiescence.

It is probable that the original ulcers in the bowel are produced by other microorganisms or factors and that *B. necrophorum* is a secondary invader.

Frank Meleney, New York City, questioned the etiologic relationship of this microorganism to the disease and was inclined to consider it a secondary invader. In a search of 40 cases of ulcerative colitis *B. necrophorum* was found in only 3 cases, but in these 3 cases good responses were obtained from zinc peroxide therapy. The microorganism was found in infectious processes remote to the colon in 9 cases which did not have ulcerative colitis.

**Observations on the Cause and Treatment of Postoperative Atelectasis and Bronchopneumonia,** Henry K. Ransom and (by invitation) Cameron Haight, Ann Arbor, Mich.—The retention of secretions within the bronchial tree is responsible for the development of atelectasis and bronchopneumonia which together constitute the chief cause of respiratory complications. Careful attention to the cough mechanism in order to provide for the complete evacuation of sputum at all times greatly decreases the incidence of these complications. An impending atelectasis or pneumonia can be recognized more promptly by physical examination than by roentgen examination. The morbidity and mortality of postoperative complications of bronchial etiology are considerably lessened by the prompt use of tracheobronchial suction when the cough mechanism is insufficient to provide adequate bronchial drainage.

Tracheobronchial suction is accomplished by passing a small catheter into the nasopharynx, and then with the tongue drawn strongly forward it is advanced into the trachea quickly during inspiration. By arranging the position of the patient the catheter can be directed into either bronchus as desired. Suction is exerted through the catheter. Occasionally it is necessary to resort to bronchoscopic aspiration.

Elliott Cutler, Boston, stated that the incidence of these pulmonary complications showed a close relationship with the degree of reduction of vital capacity following operation. Such reductions of vital capacity result from painful and other stimuli emitting from the wound. Thus, total anesthesia of the wound during the first few days by some long acting agent would do much to prevent postoperative pulmonary complications. Dr. Ransom presented statistical evidence that the type of abdominal incision (transverse versus longitudinal) does not significantly alter the incidence of postoperative pulmonary complications. Walter E. Lee, Philadelphia, believes that the incidence of atelectasis has increased as a result of more prolonged operations and advocates the routine use of aspiration of the larynx and trachea before moving patients from the operating table. Frank Lahoy, Boston, emphasized the necessity of training resident surgical staffs to meet the emergency of evacuating bronchial secretions in these cases immediately.

**The Syndrome of Mesenteric or Subperitoneal Hemorrhage (Abdominal Apoplexy),** Alton R. Kilgore and (by invitation) Glenn F. Cushman, San Francisco.—With diffusion of blood between the leaves of the mesentery there are at first annoying abdominal and back pain, soreness, restlessness, diffuse tenderness,

on the control of carcinoma of the stomach. A. W. Oughterson, New Haven, Conn., reviewed carcinoma of the stomach as a community problem. Only 57 per cent of the patients dying in New Haven of gastric cancer from 1931 to 1938 were ever admitted to a hospital; 10.7 per cent had had resections done, and 2.1 per cent of the total represented five-year cures. More attention should be paid to patients with a short history of gastric symptoms; they should be admitted immediately for study. Robert Zollinger, Boston, summarized 217 cases observed in the Peter Bent Brigham Hospital in the last ten years; 85 per cent of the patients were operated upon; the rate of resection has increased to 46 per cent in the past five years. There were 8 five-year survival (38 per cent of the resected cases). Walter O. Palmer, Chicago, emphasized the fact that the control of cancer depends upon the patient, physician, x-ray man, and the skill of the surgeon.

**The Effect of Hot and Cold Applications to the Abdominal Wall and Also Hot and Cold Fluids Administered by Mouth on Gastric and Intestinal Secretory and Peristaltic Activity.** J. Dewey Bisgard, Omaha, Neb.—The effects of hot and cold drinks and applications on peristaltic activity were determined by balloons in the stomach, small intestine, and colon. Peristalsis is markedly reduced after operations on the stomach and remains so for about a week. This suggests that the stomach acts as a "pacemaker" for intestinal peristalsis. Peristalsis is increased if ice is applied to the abdominal wall and decreased if hot packs are used. By mouth, ice water decreases peristalsis and increases the hydrochloric acid output of the stomach; hot water produces the opposite effect. If ice is applied to the extremities, peristalsis is not accelerated, but the hydrochloric acid secretion still is increased. Hot packs therefore seem to be indicated for peritonitis and bleeding ulcers.

James M. Winfield, Detroit, discussed the applications of these principles and the treatment of adynamic ileus. He uses the Miller-Abbott tube, and heat externally, but does not advise pitressin. Charles W. Mayo, Rochester, Minn., pointed out that the most effective drugs are not necessarily the most expensive.

**The Miller-Abbott Tube in Surgery.** Octa C. Leigh, Jr., and Richard O. Diefendorf, New York City.—The importance of the Miller-Abbott tube was illustrated by its use in several types of diseases. Two hundred and seven cases of uncomplicated small bowel obstruction were treated, with a mortality of 5.3 per cent. In the cases of obstruction with peritonitis, the mortality was 16 per cent if the tube passed the pylorus; if it could not be passed, the mortality was 38 per cent. The tube has been used for the treatment of ileus, and as a prophylactic against obstruction, in appendicitis, and as an adjunct to resection of the colon, especially of the right side. The Miller-Abbott tube has not decreased the mortality of strangulating obstructions, which must be recognized and subjected to immediate surgery. Of 400 attempted small bowel intubations, there has been failure in only 10 per cent.

Grover C. Penberthy, Detroit, in the discussion, emphasized the importance of the recognition of strangulation. In addition to the advantages of the Miller-Abbott tube listed by him several years ago, its value as a prophylactic against postoperative obstruction following colon resections has now been made clear.

**The Local Use of Powdered Sulfanilamide in Infections of the Peritoneal Cavity.** R. Sterling Mueller and James E. Thompson, New York City.—Intra-peritoneal sulfanilamide has been employed in 90 of the 268 cases of appendicitis treated in the Roosevelt Hospital, New York City, since January, 1940. There

## REVIEW OF THE SECTION ON SURGERY OF THE AMERICAN MEDICAL ASSOCIATION

CLAUDE E. WELCH, M.D., BOSTON, MASS.

THE following are abstracts of papers read before the Section on Surgery of the American Medical Association in Cleveland on June 4, 5, and 6, 1941.

**Carcinoma of the Stomach in a Large General Hospital, Frederick F. Boyce, New Orleans.**—Carcinoma of the stomach is a very serious problem in the Charity Hospital, New Orleans, because negroes form a high percentage of the patients. Two series of 200 surgical cases, one of which was reported in 1933, and another recent one, were compared. There has been no increase in the number of cases resected and no reduction in the operative mortality. Now of 30 patients admitted to the hospital, 10 are operated upon; 3 have exploration only; 5 have palliative operations; 2 have gastric resections. The mortality of gastrectomy is 56 per cent. This is a gloomy picture, and probably can be improved only by the careful attention of the physician, and prompt recourse to surgery, since no cooperation can be expected from the patient.

**Malignant Lesions of the Stomach: Importance of Early Treatment and Results, Waltman Walters, H. K. Gray, and James T. Priestley, Rochester, Minn.**—All of the cases of carcinoma of the stomach observed in the Mayo Clinic from 1907 to 1938 were reviewed. A third of the patients with resectable lesions had symptoms suggestive of the ulcer syndrome. Eighty-one per cent of the patients with an ulcer history had had adequate response to medical therapy. Of the resected specimens the x-ray diagnosis was carcinoma in 75 per cent, ulcer in 10 per cent, gastric lesion, unspecified, in 13 per cent, benign lesion in 1 per cent, and no lesion in 1 per cent. In 20 per cent of the cases stated by the radiologist to be inoperable or of doubtful operability, resections were possible. Of all the cases of carcinoma of the stomach admitted, 58 per cent were explored; resections were done in 26 per cent of the total. The mortality in 2,772 resections was 16 per cent. The mortality increased with age. The mortality according to type of resection was Billroth I, 11 per cent; Billroth II, 18 per cent; anterior Polya, 18 per cent; posterior Polya, 15 per cent; segmental resection, 16 per cent; local excision, 10 per cent; total gastrectomy (27 cases), 67 per cent. The survival rate (based on operative survivals) was 29 per cent at five years, 20 per cent at ten years, 15 per cent at fifteen years, 11 per cent at twenty years, and 6 per cent at twenty-five years. The five-year survival rate for lesions localized to the stomach was 45 per cent; if there was extension that was resectable, without metastasis, 39 per cent; if metastasis without extension, 17 per cent; with both metastasis and extension, 17 per cent. According to the pathologic grade, the survival rate was 86 per cent for Grade I; 59 per cent for Grade II; 30 per cent for Grade III; 23 per cent for Grade IV. The survival rate was approximately the same in all age groups.

George T. Pack, New York City, in the discussion, emphasized the fact that the skill of the surgeon is entirely secondary to an increased number of resections so far as increasing the number of five-year cures is concerned. The statistics presented by Dr. Walters, he said, formed the most optimistic report ever made.

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**The Surgical Management of Gall Bladder Disease as Correlated With New Physiologic Concepts, H. Glenn Bell and Leon Goldman, San Francisco.**—The greatest improvement in the care of patients with gall bladder disease has been due to preoperative preparation. Proper attention must be paid to the general condition of the patient; tests of hepatic and renal function must be made. The preoperative diet should be high in carbohydrates, adequate in protein, low in fat, and should contain all vitamins, especially vitamin K. Fluid and electrolyte balance must be maintained. The proper time to operate must be chosen, preferably when jaundice has disappeared or has reached a level. Anoxia must be avoided during the procedure. Proper sedation kept at a minimum level, the use of cholangiography, and attention to the sphincter of Oddi are other important operative details. Postoperatively, bile salt therapy may be of importance. The statistics of the University of California Hospital for the past ten years were summarized. The over-all mortality in 435 cases was 2.5 per cent. Cholecystectomy in the chronic state (290 cases) carried a mortality of 1.4 per cent; cholecystectomy for acute cholecystitis, 3.8 per cent; common duct exploration, 5.8 per cent; and cholecystostomy, 0 per cent. The common duct was explored in about 20 per cent of the cases; it was done rarely below the age of 50 years, but frequently thereafter. An 11 per cent incidence of stones in the common duct was found. Only 1 patient who had had a primary duct exploration had to have a second. The results of cholecystectomy showed 93 per cent cured if stones were present, contrasted to 61 per cent of patients cured if there was chronic cholecystitis without stones.

Warren H. Cole, Chicago, in the discussion, stated that persistent pain after cholecystectomy is usually due to a wrong preoperative diagnosis. Infection of the gall bladder is usually chemical, rather than bacterial. He believes operation on the acute gall bladder is indicated if the temperature has not returned to normal in thirty-six hours after admission, or if the signs of infection increase.

**The Use of Cotton as a Suture Material, With Particular Reference to Its Clinical Application, William H. Meade and Carroll H. Long, New Orleans.**—Cotton was shown to incorporate the qualities of pliability, satisfactory tensile strength, a high coefficient of friction, stability on exposure to heat or moisture, and the failure to produce any great tissue reaction. The cotton sutures are sterilized by boiling twenty minutes or by autoclaving. They have been used in all types of wounds where interrupted sutures could be used and are particularly valuable in contaminated wounds. Sizes 50 to 80 may be used for ligatures. Heavy mercerized cotton is employed in ligating the pulmonary artery, etc. Since adoption it has been used in about 1,800 cases in the Charity Hospital. The percentage of infection in clean and contaminated wounds has been distinctly lower than that when catgut was used, and appreciably lower than silk. Thus of clean wounds, 4.5 per cent of the cotton, 5.1 per cent of the silk, and 19.3 per cent of the catgut became infected. Of the contaminated, 22.4 per cent of the cotton, 70.6 per cent of the silk, and 100 per cent of the catgut, developed infection. There is a tremendous financial saving when cotton is used. Comparative costs of each suture material if each were used exclusively in the Charity Hospital during one year would be cotton, \$15; silk, \$573, catgut, \$6,528.

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were no deaths. This included 31 cases of acute appendicitis, 18 with abscess, and 41 with peritonitis. One case of jaundice was observed, but there were no other complications ascribable to the drug. In a control series of 742 cases from 1935-1939, there were 21 deaths of which 13 were due to peritonitis. This was a mortality rate of 0.53 per cent for simple acute appendicitis, 6.78 per cent for appendiceal abscess, and 11.96 per cent for appendiceal peritonitis. The sulfanilamide was sterilized by dry heat for two hours at 140°. In severe infections, the maximum dose used has been 18 Gm., of which two-thirds was placed in the abdominal cavity and one-third in the wound. The usual dose was 175 mg. per kilogram of body weight. Drainage was employed in the usual fashion. Absorption is maximum about twelve hours after operation, although the drug can be detected in the blood twenty minutes after operation, and persists about 200 hours. No bad effect on wound healing was observed. In 16 cases, administration was continued after the operation.

**The Use of Sulfanilamide in the Peritoneum: Experimental and Clinical Observations,** Howard C. Jackson and Frederick A. Collier, Ann Arbor, Mich.—The authors found that sulfanilamide, implanted intraperitoneally in dogs, provided a peak blood concentration in three hours, regardless of the amount of the dose. Mixing with gum acacia did not slow the rate of absorption. If the drug is given by mouth, the blood level is still rising at the end of twenty-four hours. Clinically, intraperitoneal implantation has been done in 67 instances (33 colon operations, 15 stomach and small bowel resections, 12 perforated appendices, and 5 of other peritoneal infections). The dose was usually 5 Gm. Twenty-nine of the patients had chemotherapy by mouth as well. Postoperatively only 5 cases showed evidence of peritonitis; it was felt that too little drug was given to 3; a pelvic abscess developed in 1. Jaundice did not appear in the patients who received only intraperitoneal implantation, but did in 31 per cent of those who received additional oral chemotherapy. No fatal results occurred from this complication. It was also proved experimentally that concentration in the portal blood is much higher than in the jugular for the first four hours after implantation. Sulfanilamide crystals could be found up to two hours after implantation, while after four hours the peritoneum appeared entirely normal.

Several additional features were mentioned in the discussion. Henry W. Cave, New York City, pointed out that sulfanilamide is a safe and effective agent to reduce peritoneal infections when given intraperitoneally; 4 to 6 Gm. are placed about intra-abdominal anastomoses. It will not, however, prevent all deaths. A traumatic perforation of the sigmoid with general contamination of the peritoneal cavity recovered uneventfully following immediate laparotomy and the use of sulfanilamide. Alton Ochsner, New Orleans, has not obtained as good results. He believes the drug should not be used unless there is a gross contamination. If it is to be used intraperitoneally, drainage should be omitted. He warned against the intravenous use of sulfathiazole, because of 2 cases of optic atrophy that followed. He suggested the possibility of small doses, with repetition a few hours later. James E. Thompson, New York City, cited the use of intraperitoneal sulfanilamide in 99 large bowel operations, with 8 deaths. It was also used as a therapeutic measure in 20 desperate cases of peritonitis with 6 deaths. Dr. Collier stated that no evidence of harm to the peritoneum from sulfanilamide has been discovered. The drug is not a panna, and other surgical principles should not be forgotten just because it is used. It is not wise to use it in clean cases, such as radical mastectomies. Contaminated wounds are preferably treated by secondary closure of the fat and subcutaneous tissue. Frederick L. Reichert, San Francisco, experimentally has found no reaction from sulfanilamide in the peritoneum or



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**Embryoma of the Kidney (Wilms' Tumor),** William E. Ladd and Robert R. White, Boston—A series of 60 cases of embryoma of the kidney observed in the Children's Hospital was discussed. It is a disease of the first 3 years of life. The tumors vary greatly, histologically. They are nearly always radiosensitive. Immediate operation, without preoperative x-ray therapy, is advisable, because of the danger of early metastasis. A preliminary pyelogram is taken to be sure of the presence of a normal contralateral kidney. The transperitoneal approach is preferred. The renal vessels are ligated before any mobilization of the tumor is done. The perirenal fat is removed with the kidney. Of the 60 cases, the operative mortality was 3.3 per cent, 18 patients are still living, 14 of them being probable cures. Recurrence always was noted before the eighth postoperative month, if it was to occur, except 1 case that recurred at twenty months. A two year cure therefore seems to be significant. The size of the tumor does not appear to alter the prognosis, but younger patients have a better outlook than older. Postoperative x-ray for recurrence is of palliative value, but will not destroy all the tumor cells.

James T. Priestley, Rochester, Minn., in the discussion, stated that of 39 patients treated in the Mayo Clinic, there are 6 (15 per cent) five year cures. He believes x-ray is of value before operation in order to diminish the size of the tumor, and also after operation. Monroe Wolf, New Orleans, presented microscopic slides of several cases observed in the Charity Hospital recently.

**Diagnosis, a Responsibility of the Surgeon, Chairman's Address**—The chairman's address was read by Lloyd Noland, Parkfield, Ala. He emphasized the fact that diagnosis has often been relegated to the physician, the surgeon thereby merely carrying out the technical procedure. There has been undue emphasis placed upon operative details by surgeons. The surgeon's hand still remains the most important diagnostic tool; the history and other diagnostic methods cannot be neglected, but the surgeon's examination is the most valuable.

**Cancer of the Lung of Long Duration,** Alfred Goldman, San Francisco—Case histories were cited indicating that cancer of the lung may have a long clinical course. Eleven cases were found in which the disease lasted more than two years. Adenomas occurred chiefly in young women, carcinomas in older males. Peripheral circumscribed tumors grow more slowly and offer the best chance for surgical cures.

**The Surgical Approach to Hypertension,** Geza de Takats and Howard E. Heyer, Chicago—De Takats has employed supradiaphragmatic, infradiaphragmatic, and transdiaphragmatic splanchnic nerve sections, vascular implants to the kidney, and nephrectomy. On the splanchnic nerve sections, the transdiaphragmatic section of

Smithwick gave the only real reductions of high blood pressure. The value and place of vascular implants to the kidney are still unclear. Nephrectomy in one case was successful for at least ten months. Early cases of hypertension respond most satisfactorily; the operation was of no value in malignant hypertension.

Reginald H. Smithwick, Boston, described his technique. He has found that of 66 cases with partial denervation of the splanchnic bed, only 9.1 per cent had good results. Of 38 cases with complete splanchnic denervation, 71 per cent had significant and persistent lowering of the blood pressure. Several of these greatly improved patients had malignant hypertension. Peter Heinbecker, St. Louis, doubted the necessity of so extensive denervation in early cases. E. A. Kahn, Ann Arbor, Mich., pointed out that of 700 cases operated upon by Peet's supra-diaphragmatic approach, 33 per cent are living five years afterward.

**Phlebitis and Pulmonary Embolism,** Claude E. Welch and Henry H. Faxon, Boston.—The methods of therapy of phlebitis were considered. Emboli occurred in one-third of the patients who had deep phlebitis of the leg, and fatal emboli in 1 out of 25. The incidence of fatal emboli increased with age. The venogram is valuable as a means of diagnosis. Ligation and division of the saphenous vein is recommended for acute superficial phlebitis. For deep phlebitis, ligation and division of the femoral vein in patients over 40 years of age is indicated. Below that age, conservative measures should be supplemented by novocain injection of the lumbar ganglia. Ligation is indicated at any age if infarcts have occurred. In a group of 33 patients who have had ligation of the femoral vein, in whom there were thirty-six preoperative infarcts, only one probable infarct has been observed since operation.

Alton Ochsner, New Orleans, in the discussion, emphasized the importance of distinguishing thrombophlebitis and phlebothrombosis. In the former, relief of temperature and edema is rapid after novocain block. Pain is permanently relieved in 90 per cent of the patients after the first injection, while the fever subsides in 64 per cent of the cases within forty-eight hours. It is in the latter group that one must be on guard for pulmonary emboli, and it is here that vein ligation is important. Conrad E. Lam, Detroit, has treated phlebitis and pulmonary infarcts with heparin since April, 1939. Thirty-two patients who had had emboli recovered without further incident. One had a fatal embolus after treatment. Heparin can now be given cheaply enough to justify its use. Dr. Faxon pointed out that only 5.5 per cent of patients with fatal emboli have demonstrable phlebitis. It is therefore important that more attention be paid to the diagnosis of asymptomatic thrombosis that precedes fatal emboli.

**The Mechanism of Delayed Wound Healing in the Presence of Hypoproteinemia,** Jonathon E. Rhoads and M. T. Fliegelman, Philadelphia.—Studies on wound healing were presented. In the presence of hypoproteinemia, fibroplasia is markedly slowed in the experimental animal, provided the deficiency is produced by a low protein diet or plasmapheresis. However, if the hypoproteinemia is produced by repeated infusions of aecia solution, or if aecia is administered to dogs with low protein levels, the fibroplasia may be brought back nearly to normal. Thus nearly normal healing has been observed in some animals, in whom the serum protein was only 1.9 per cent.

Charles G. Johnston, Detroit, stated that in his cases most wound disruptions occurred in patients who had gastric or duodenal disease with diets low in vitamin C and protein. There is no therapeutic indication for the administration of gum aecia postoperatively. I. S. Raydin, Philadelphia, emphasized the necessity of maintaining the anatomical and physiologic integrity of operative wounds.

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followed by implantation of 5 to 20 Gm. of sulfanilamide. The wounds were closed unless they were over twelve hours old, or if there was too much soft tissue damage to allow closure. Postoperatively, sulfathiazole was given at the rate of 1 Gm. every four hours as soon as nausea ceased. It was found that the percentage of nonunion was not influenced by sulfanilamide. The incidence of pyogenic infection has been reduced from 33 to 18 per cent. In the cases that became infected, the infections were not so severe as they were before sulfanilamide. The use of sulfanilamide has greatly increased the number of primary open reductions and closures.

Harold R. Bohlman, Baltimore, in discussion, emphasized the treatment of shock and the use of local or regional block, and careful wound toilet. He believes bullet wounds should be opened and carefully cleaned. Entirely too much tissue has been removed by débridement. Tension must be avoided at all times, especially since gas gangrene develops as a result of disturbance of circulation. J. E. Cannaday, Charleston, W. Va., has found markedly improved results with compound fractures from the use of sulfanilamide.

**The Splinting of Compound Fractures, Frank J. Cox, New Orleans.**—The various methods of splinting that may be employed for compound fractures were described in detail. For the lower extremity, the Thomas splint with the clove hitch for traction is used. The hitch should be replaced by a skewer through the bottom of the shoe if traction is to be continued for some time. Fixed traction in open splints may be maintained by means of two pins attached to the Thomas splint. Russels' traction is to be continued for some time. Fixed traction in open splints may be maintained by means of two pins attached to the Thomas splint. Russels' traction is not advisable for compound fractures since dressings are difficult. For the upper extremity a Jones arm splint may be used for transportation traction. Traction through the olecranon is often valuable. Roger Anderson's multiple pin method was discussed.

H. A. Swart, Charleston, W. Va., illustrated a new splint he has developed for the upper extremity.

**Chemotherapy in the Treatment of Compound Fractures, Rex L. Diveley, Kansas City.**—Dr. Diveley presented his plan of therapy for osteomyelitis—oral administration of sulfathiazole to produce a blood level of 5 mg. for several days, followed by a thorough local operation, with local implantation of sulfathiazole, wound closure, and postoperative oral administration of the drug, usually for two weeks. Fifty-six cases have now been treated that way, of which 16 were compound fractures. Of the series, 53 healed by primary intention, 2 others healed, but extremely slowly, and 1 case was a failure. The average total dose of sulfathiazole was 57.4 Gm., the blood concentration, 4.3 mg. per cent; the amount of drug implanted locally, 1.9 Gm.; and the healing time, 21.6 days.

Francis M. McKeever, Los Angeles, in discussion, stated that 71 per cent of 73 patients with large wounds and compound fractures developed infection. When chemotherapy was employed in a similar group, 6 cases remained clean while only one became infected. Robert W. Johnson, Jr., Baltimore, advised the use of sulfanilamide in compound fractures treated early, since the gas bacillus and streptococcus are the most dangerous contaminants; in late cases, where they are known to be absent, sulfathiazole is better.

**Similarities and Distinctions Between Shock and the Effects of Hemorrhages,** Virgil H. Moon, D. R. Morgan, Marshall M. Lieber, and Donald J. McGrew, Philadelphia.—The clinical manifestations of shock and hemorrhage are identical in many respects, but there are important differences. Shock is marked by an increased flow of lymph due to leakage of plasma through capillary walls. Edema, serous effusions, and visceral petechiae occur, while they are not found after hemorrhage. During shock the urine volume is decreased and contains albumin, red cells, and casts; during or after hemorrhage no characteristic changes occur. In shock, the red blood cell count is increased, while it is decreased after hemorrhage. It is suggested that contradictory findings have been obtained by other investigators because of the use of anesthetics during experiments. It is also to be noted that for animals in shock, a little hemorrhage is very dangerous.

Henry H. Harkins, Detroit, discussing the paper, stated that it is his belief that hemorrhage and shock are not the same, but that hemorrhage may lead to shock. Thus transfusions are not effective in the late stages of hemorrhage, just as the case is with shock. If the blood pressure is kept down for long periods from hemorrhage, the changes at autopsy are the same as those of shock. Even if shock differs from hemorrhage, from the point of view of the patient it makes little difference, since restoration of fluid is the only therapeutic measure available.

**Traumatic Rupture of the Intestine Due to Nonpenetrating Wounds of the Abdomen,** D. Henry Poer and Ira A. Ferguson, Atlanta, Ga., and Edward Wolliver, Cincinnati, Ohio.—In a series of 1,476 cases in the literature, the total mortality was 72.1 per cent; the operative mortality in the 1,014 subjected to surgery was 59.5 per cent. Thirty-six cases were observed by the authors. Prompt operation was shown to be essential. Abdominal pain and tenderness were the most important symptoms. They were often insignificant at first, but increased rapidly. Nausea was the next most common symptom. The pulse rate rises steadily. Free gas under the diaphragm was rare. External evidence of injury was present in only 16 out of the 36 patients. A decision for operation must often be based on intelligent suspicion. The important operative procedures are closure of perforations, resection, and exteriorization.

W. L. Estes, Jr., Bethlehem, Pa., in the discussion, said that the low incidence of this lesion is shown by the fact that only 1.4 per cent of the cases in his clinic were those of abdominal trauma. The cases are divided into three groups. In the most severe no operation is indicated; in another, the diagnosis is easy, and immediate operation done. In the last the diagnosis is difficult. These patients must be observed by the same, competent surgeon, and a blood count made every thirty minutes. No opiate is to be given. The type of trauma that is most to be feared is a circumscribed blow, a kick or a fall against a projecting object.

**Fresh Compound Fractures: Treatment by Sulfa-Drugs and by Internal Fixation in Selected Cases,** Willis C. Campbell (deceased) and Hugh Smith, Memphis, Tenn.—The therapy employed in a series of 143 patients with compound fractures was débridement, irrigation, implantation of sulfanilamide, and closure of the wound, with internal fixation if indicated. Internal fixation was used in 42 cases; it is recognized that this enhanced the risk of nonunion, although it had no adverse effect on infection. The cases were divided according to severity of the injury. In the mild cases superficial débridement was done and the wound cleaned, but not enlarged. Pistol shots were treated as closed fractures; no probing was done for the bullet. Shotgun injuries, on the other hand, were usually associated with severe fractures. For moderate and severe cases complete deep débridement was

**Williams' Obstetrics: A Textbook for the Use of Students and Practitioners.**  
By HENRIUS J. STANDER Ed. S. Pp 1,401, with 704 illustrations. New York,  
1941, D Appleton Century Co.

This eighth edition, Stander's second revision, of Dr Williams' textbook on obstetrics continues the classic presentation of its subject matter. While much of the material has been completely revised, it retains unmistakable earmarks of Dr. Williams' style and ease of presentation. In spite of the publication of several other texts on obstetrics during the past ten years, this one persists in being head and shoulders above any other. It is ideal for the student and practitioner as well. For those not interested in historical data and theoretical considerations, these are now easily separated since they appear in small type.

Many of the original illustrations have been replaced and a host of new ones appear, all from the hand of a competent medical illustrator. The text itself has been almost completely rewritten, with the result that little of the original remains unaltered. The section on embryology now conforms to the newer ideas of Streeter and Hartman. The mechanism of labor embraces the roentgenologic findings of Caldwell and Maloy. The toxemias of pregnancy are classified and discussed according to the new classification of the American Committee on Maternal Health, a step in the direction of ultimate national standardization of the criteria for diagnosing these diseases. Roentgenologic pelvimetry is discussed in detail. The treatment of puerperal infection and certain other infectious processes complicating pregnancy and the puerperium includes the newer concepts of chemotherapy. The chapters on diseases of the urinary system and endocrinology have been virtually rewritten. Thus, this revised edition has been brought up to date with all recent advances pertaining to physiology and pathology of gestation and to medical and surgical complications of pregnancy and the puerperium.

**The Role of the Liver in Surgery** By Frederick T. Boyce, M.D. Pp 365, with  
44 illustrations. Springfield, Ill., 1941, Charles C Thomas, Publisher. \$5.00.

Boyce's monograph, *The Role of the Liver in Surgery*, in 1940 was awarded the quinquennial Samuel D. Gross Prize for research in surgery by the Philadelphia Academy of Surgery. The monograph was published in accordance with the stipulations of the Samuel D. Gross Prize Award. As stated in the preface, one of the stipulations of this award is that the monograph shall be the report of the research work of a single individual. As also stated in the preface, it was the express desire of the Gross Prize Committee of the Philadelphia Academy of Surgery that the monograph be presented exactly as submitted, on Jan. 1, 1940, except for minor editorial changes and the addition of new work on the bleeding tendency in newborn children (Chapter VIII).

This monograph places timely emphasis on a number of important aspects of liver function and liver disease, particularly as they relate to surgery. For example there is an excellent discussion of the hepatorenal syndrome, which is a relatively frequent postoperative hepatic complication and which has not been given sufficient attention in the past. The relation of sulfanilamide to the production of liver damage and jaundice, both before and after operation, is quite properly stressed. This section of the monograph contains a well rounded discussion and survey of the literature on so called "postoperative liver death."

Considerable attention is given to the subject of assaying liver function. Boyce's past studies, as summarized in the present monograph, have dealt chiefly with the hippuric acid test. The relative merits of various methods of carrying out this test, together with the description of the actual technique, are thoroughly considered. There is no doubt that the hippuric acid test is distinctly worth while, yet its relative value may have been somewhat overemphasized in this monograph. Boyce has evidently employed but two other methods of testing

## Book Reviews

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**Surgery of the Hand.** By R. M. Handfield-Jones, M.C., M.S., F.R.C.S. Pp. 135, with 95 illustrations, including several in color. Baltimore, 1940, Williams and Wilkins Co. \$4.50.

This readable little book has been clearly and concisely written. It is primarily for the general practitioner and, therefore, somewhat didactic in nature. The anatomical descriptions and drawings are clear and concise, and elucidate some points which most authors have left a little cloudy. In a few respects, the author's advice is counter to the practice in this country, such as in swabbing lacerations with iodine, omitting elevation of the extremity in lymphangitis, and elimination of toxins of infection by purgation, but on the whole, the therapy is excellent.

This book makes a pleasant evening's reading, and is indexed for reference purposes. It should be of value, both to the student and to the practitioner.

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**Age Morphology of Primary Tubercles.** By Henry C. Sweany, M.D. Cloth. Pp. 258, with 73 illustrations. Springfield, Ill., 1941, Charles C Thomas, Publisher. \$5.00.

This is a monograph of 252 pages, extensively illustrated with charts, reproductions of roentgenograms, and many excellent photomicrographs; it is the product of a great deal of painstaking pathologic work correlated with careful analyses of case histories.

Sweany's thesis is that primary tubercles, over a period of years, go through a morphologic evolution, whose stages follow, within certain limits, a definite time schedule. By studying primary lesions at post mortem in the lungs of individuals whose original contact with tubercle bacilli can be dated with fair accuracy, he constructs, in the first three chapters, a timetable for the pathologic changes which take place in these tubercles.

The next four chapters apply this timetable by estimating from it the age of calcified primary foci found at necropsy, and thus attempting, for example, to date the initial infection of an individual whose history indicates two or three separate episodes, one of which may have represented the occurrence of a primary lesion. Finally, a series of living patients is presented, in whom, through serial roentgenograms, it is possible to follow the evolution of primary infections of various types; and the author attempts to correlate these x-ray changes with the pathologic data presented earlier, but recognizes that this can be done only to a very limited extent.

In summary, then, this monograph describes a remarkably complete pathologic study of "first infection" tuberculosis, and an interesting new approach to the subject through analysis of age morphology. It seems possible that the method may become useful as a tool in studying the pathogenesis of tuberculosis in certain well-documented cases. At present (as the author himself states), this work has very little practical clinical application, but it teaches at least one valuable clinical lesson: the old calcified tuberculous focus which one assumes to be "healed," undergoes changes for many years, and in the process, it may under some circumstances become potentially dangerous as a source of endogenous reinfection.



# SURGERY

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## Original Communications

### CEREBRAL ANGIOGRAPHY\*

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AMONG the procedures for exploration of the central nervous system and, particularly, of the brain, we must include angiography.

It was in 1926 that Dr. Egas Moniz, the present Professor of the Medical School at Lisbon, conceived the idea of extending radiographic exploration to the study of the arteries of the brain by the introduction of some harmless substance of greater opacity than the mineral salts of the skull. In this way he hoped to picture the anatomicofunctional arrangement of the arteries. The term radiodiaphoric method (*método-radio-diaphorico*) was proposed when it was applied to the brain.

He began by filling glass tubes, approximately equal in diameter to the cerebral arteries, with solutions of sodium iodide and other metallic salts in various concentrations. These tubes were introduced into the cranium of a corpse and x-ray pictures made immediately. He found that the tubes became better visualized the greater the concentration of the solution. After adopting a definite strength of solution, capable of giving the desired contrast, he continued his experiments on corpses, and not without great difficulty succeeded in obtaining the first arteriogram of the brain. This, while satisfactory for the study of topographical anatomy, did not fulfill his hopes. Not wishing to abandon the idea, he continued with analogous experiments in living animals (dogs, cats, monkeys, etc.) with the intention of applying this new method to the diagnosis of diseases of the brain in the human being. Further experiments enabled him to select a harmless solution of sufficient opacity for use in the clinic. On June 28, 1927, for the first time he injected into a patient 6 c.c. of 25 per cent sodium iodide solution and obtained the first

\*Read before the meeting of the Society of Neurology and Neurosurgery in the Neurological Institute, Montreal.

Received for publication, Feb. 6, 1941.

liver function; namely, the bromsulphalein and the bilirubin tolerance tests. Neither of these, of course, are of much, if any, value in the patient who is more than a little jaundiced. All three of the tests are sufficiently involved that they are not well suited to serial study. In this respect, more emphasis might well have been placed upon the value of serial qualitative urine urobilinogen tests. Boyce recognizes that it is impossible to rely upon any one test alone in the clinical study of liver function.

The monograph contains an excellent discussion of the hemorrhagic tendency in jaundiced patients, and its treatment by vitamin K. Included in this discussion is a summary of Boyce's studies of the serum volume index. These have aided greatly in clarifying the relationship between hypoprothrombinemia and the defective clot formation in jaundice.

The importance of fatty liver in increasing postoperative mortality is touched upon briefly by mention of Ravdin's important studies of this question. Some discussion of the relation of riboflavin, cholin, and lipoeic to the problem of fatty liver might well have been included.

The material composing the monograph is well organized, and the illustrations are clear, and, for the most part, well selected.

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**Clinical Urology.** By O. S. Lowsley and T. J. Kirwin. Two volumes, pp. 1684, with 365 illustrations. Baltimore, 1940, Williams & Wilkins Co. \$10 per set.

These books cover their field quite adequately. While the introduction recommends them particularly to medical students, general practitioners, and general surgeons, they will repay study by the urologist as well. The two outstanding features are the wealth of excellent illustrations by Didusch, and the rather extensive bibliographies. These two alone are worth the cost of the volumes.

There are excellent sections on diagnostic roentgenology, the simpler laboratory procedures, anesthesia, and irradiation therapy, in addition to the customary discussion of history taking, general and special instrumental examinations, and the various diseases and disorders. Surgical therapy is covered about as thoroughly as possible considering the size of the books. The discussion of prostatic surgery is remarkably temperate and sound, if one ignores the authors' recommendation of subtotal (semiradical) perineal prostatectomy in certain cases of benign hypertrophy.

The relation of diet and urinary pH to lithiasis and infection are covered.

Lest the reader suspect that the reviewer is in the pay of the authors or publishers, it is well to point out certain defects in the work. One might, I think, be justified in drawing attention to a noticeable tendency to over-emphasize the works, instruments, and pet contraptions of the authors, although one must admit that others are there, too. The old fable of the danger of sudden emptying of the bladder is again handed down to posterity, together with the standard apparatus for its prevention (or for salving the physician's conscience if anything goes wrong!). Neurogenic vesical dysfunction is inadequately discussed. One could also wish that publication had been late enough to permit a discussion of sulfapyridine and sulfathiazole in gonorrhea.

Toward the end of 1931 there appeared a product which consisted of a 25 per cent solution of thorium dioxide which promised to give a greater contrast in the radiographic exploration of fistulas and the organs for which it was recommended; i.e., renal pelvis, ureter, bladder, and urethra. Warning was given that its intravenous administration was contraindicated. When Egas learned of this new preparation and observed the satisfactory contrasts which were obtained with it, he carried out repeated experiments on the possibility of injecting it intra-arterially without danger, and finally decided to utilize it in clinical cases.

On Dec. 5, 1931, he and his co-workers published their first work on the use of thorium dioxide for cerebral angiograms.<sup>3</sup>

From this date on, he has abandoned the use of sodium iodide and has substituted the colloidal suspension of thorium dioxide. The greater tolerance of the organism for this preparation permits greater quantities to be administered and, consequently, allows clearer and brighter pictures. This allows us today to obtain cerebral arteriograms of great utility in the diagnosis, localization, and delimitation of lesions of the brain.

#### CEREBRAL PHLEBOGRAPHY

On Dec. 19, 1931, Egas accidentally succeeded in obtaining the first cerebral phlebogram. After injecting the thorotrast (*dioxido de torio*) into the common carotid artery, the roentgen operator delayed in making the plate and, when it was developed, it was observed that the cerebral veins had been photographed. The development of cerebral phlebography has been brief, since, after this accidental find, it was not possible to obtain systematic radiographs of the cerebral veins until Nov. 11, 1935.

Egas' work on cerebral phlebography was crystallized in a monograph published in 1934.<sup>4</sup> Since then cerebral phlebography has been considered as a necessary complement to complete angiographic exploration of the brain. Careful studies show that the venous circulation of the brain has two very distinct phases, the first and second, which are distinguished by the various venous groups which the radiographic plate registers. Thus, in the first phase the ascending and descending veins are involved and in the second, the superior longitudinal sinus, the ampulla and veins of Galen, the straight sinus, the lateral sinus, the torcular Herophili, and the veins of Labbé.

After this brief résumé in which have been noted the priority of the discovery and the development of the complete angiographical technique of the brain by Egas, I am happy to state that in 1935 at the congress held in Sweden by the Neurological Surgeons, the committee of the Neurological Society of Great Britain resolved to express to Professor Egas its satisfaction and thanks for his great service to

arteriograms without observing the least disturbance from the injection. Encouraged by this success, he continued with his experiments and at the same time attempted to simplify the surgical technique for injection of the opaque solutions.

In July, 1928, the Neurological Society (*Société de neurologie*) of Paris in the first number of its review published a paper by Egas<sup>1</sup> on radiodiaphoric methods in the localization of cerebral tumors.

At this time he had already obtained fifty arteriograms by injecting the opaque preparation into the common carotid without any accidents occurring, but with a more complex surgical technique than the one we employ today, since transitory ligatures of the external and common carotids were necessary in order to insure that the whole quantity of liquid injected would pass only to the cerebral blood vessels.

From 1927 until 1931 he continued his experiments uninterruptedly, trying different positions of the head, since, according to the greater or lesser inclination of the cranium in relation to the horizontal plane of the x-ray plate, the results obtained varied in regard to the greater or lesser precision of the arterial outlines. The technique was improved by degrees until arteriograms of great utility in the diagnosis of cerebral tumors were obtained.

For this he made use of every resource; for example, when a patient clinically diagnosed as having a cerebral tumor died, he immediately injected into the common carotid 8 c.c. of a 100 per cent solution of sodium iodide, obtaining immediately two x-ray pictures for comparison with those which had been obtained from patients diagnosed as "mental cases" but in whom the arrangement of the arteries had been considered normal.

In 1931, and after repeated studies carried out *in vitro*, he concluded that the sodium iodide solution did not become diluted in the arteries but preserved its concentration almost intact. Later on, Reinaldo Dosantos, Egas' collaborator, praised the use of abrodil as a substitute for sodium iodide and used it in a 45 per cent solution. They made their first trial with this new contrast medium, injecting it into the common carotid of a patient diagnosed as having a cerebral tumor which could not be localized clinically. With the arteriograms obtained by this technique they were able to make a diagnosis of frontal lobe tumor. In the same year the Japanese professors, Makoto Saito and Kazunori Kamizawa,<sup>2</sup> prepared different formulas, all with a base of lipiodol, and got satisfactory results according to their description.

From what has preceded, one can realize that all the investigators have tried to arrive at a simpler surgical technique and sharp radiographic exposition and to substitute for the radio-opaque solution some other preparation which might be better tolerated and which might also give better x-ray pictures.

in making just one injection suffice for taking the three radiograms of arteries, small veins, and large venous trunks.

The operative technique is as follows: The patient is prepared on the x-ray table. Local anesthesia is obtained by injecting about 10 c.c. of a solution of novocain, sulfate of potassium, and adrenalin; only for very agitated patients or children is general anesthesia necessary. An incision of from 2.5 to 3 cm. is made in the neck parallel to the collar bone, about 3 or 4 cm. above it and about 4 or 5 cm. from the midline, corresponding approximately to the space which exists between the two heads of the sternocleidomastoids. In general, it is easy to recognize it by simple inspection or in obese subjects by palpation. It is advisable to make the incision coincide with one of the creases in the skin of the neck so that the scar will be less evident and, after some time, almost invisible. The incision is made through the skin, the subcutaneous tissue, and the platysma, leaving open the little triangle formed by the two fascicles of the sternocleidomastoids and the collar bone.

With curved scissors, the points of which fit together perfectly and have no rough seam, one proceeds with the dissection of the fascicles of the sternocleidomastoids, introducing the scissors between the two and spreading them. This maneuver is repeated until the carotid sheath is exposed, when two retractors are placed in the incision and separated, with the object of exposing the bottom where the neurovascular packet runs. Thus, it is easy to recognize the common carotid artery by its pulsation. The artery is now punctured without opening the fascia of the vascular packet.

This done, one places under the head of the patient any appliance which will allow the impression of three or more plates without changing the position of the patient. We use with success the *escamoteador* designed by Moniz, consisting of a box with an aluminum lid in which are placed three *chaises* containing the x-ray plates and separated from each other by lead plates. The small cost of this apparatus is an advantage and it fills in every manner the uses for which it was constructed. Nevertheless, we know of another apparatus with an American patent capable of exposing seventeen films with an interval of a second between each, but its great cost does not make it very practicable in Spain.

The patient's head is placed on the *escamoteador* and must be kept in good position, which can easily be obtained by passing over the head a wide gauze band. The face rests on the dry plate, the side exposed being marked on the plate with an initial.

At the moment when the x-ray operator starts the roentgen-ray machine, the surgeon introduces the needle into the artery and rapidly injects the colloid contained in the syringe. During the injection one of the assistants must watch carefully the volume of thorotrast which

science and for his valuable contribution to our knowledge of the physiology of the intracranial circulation.

#### TECHNIQUE

During my stay in the Montreal Neurological Institute, I was charged for eight months with the study of the collateral circulation of the brain with the purpose of investigating the possible formation of softened zones by ischemia which was artificially produced by ligation of different vessels with silver clips, carefully placed in order not to provoke local anatomical alterations. In order to carry out these experiments it was necessary to resort to cerebral angiograms which were obtained by injecting into the common carotid arteries of cats and medium-sized monkeys a colloidal suspension of thorotrast. In order to obtain complete and exact knowledge of the technique I was advised to go to the clinic of the Medical School at Lisbon under the direction of Professor Egas. I worked for nine months in this school, attending a special course of twenty-five lessons on cerebral angiography given by Mouiz, who not only gave me his valuable personal cooperation but, in addition, was kind enough to place at my disposal the aid of his personnel and clinical material with which I was able personally to make numerous cerebral angiograms on human beings.

Since my return I have felt the desirability of demonstrating the utility which I believe this new method has for the careful study of neurological cases since, despite its harmlessness and ease of execution, it has not entered into the common practice of the doctors of this country. I have been fortunate in having inspiration and financial help from my teacher, Professor Cardenal; sound advice and affectionate clinical collaboration from the illustrious exponent of neurology in Spain, Dr. G. Lafora; the experience of his specialty as professor of radiology from Dr. Martín Crespo; and the unselfish help of my friends, Assistant Professor Diaz Sarasola and Dr. Escanciano.

The generic name angiograms has been given to the complete set of x-ray pictures of the arteries, capillaries, and veins of the brain after a previous injection to make them visible. Thus, for an angiogram to be complete it should consist of three parts: arteriography, phlebography of the first phase, and phlebography of the second phase.

The proof given by cerebral angiography is unquestionably of great value because of the diagnostic indications which it offers us. Its technique is of such simple execution that any general clinician, with even average surgical education, will be capable of performing it with all probability of success. It consists in injecting intra-arterially into the common carotid 18 c.c. of thorotrast. The only difficulty presented in practice is lack of strict teamwork among those who take an active part in the test. The procedure must be perfectly synchronized to succeed

With reference to the localization of cerebral tumors, the angiograms orientate us by giving data concerning the displacement of the arteries and veins of the brain, occasioned by the increase of volume in the zone where the tumor lies.

#### NORMAL ANGIOGRAPHY

In the preceding discussion the history and technique of cerebral angiography have been given; here I shall describe as clearly as possible and with the aid of illustrations the picture of a normal angiogram, with the object of facilitating an understanding of the material to follow. I shall treat only of lateral projection, which is the one that interests us most in diagnosis, because it is here that one sees most clearly the alterations and deviations which the cerebral vessels undergo and from which the diagnosis is deduced.

Consequently, I shall discuss arteriography and normal first and second phases of phlebography, simplifying the sketches as much as possible, but without omitting in them any data which might have importance or the absence of which might falsify the vascular position and relationships.

1. *Cerebral Arteriography.*—In the arteriographical images the internal carotid artery is presented, in its cerebral portion describing some curves called carotid siphon.

In the majority of cases the carotid siphon is a double siphon, determined by the undulations of the internal carotid artery; in some instances this siphon may not be completely double.

From the carotid siphon there emerges a very short artery, the artery of Sylvius, which immediately after its starting point divides into three branches; the posterior temporal artery, which is the artery with a curvature; the middle artery; and the posterior parietal artery. These three arteries form what we call the Sylvian group, whose position is of great interest to the diagnostician. In Figs. 1 and 2 we can clearly see the three arteries, which appear grouped and follow a horizontal plane.

There also emerges from the internal carotid the anterior choroidal artery under the artery of Sylvius and at the height of the emergence of the carotid siphon. At about the same level there emerges the ophthalmic artery, small in normal cases, but of extraordinary diagnostic importance. Continuing with the carotid siphon, there appears in the arteriographical images the anterior cerebral artery, which describes a curve of posterior concavity, continuing with the pericallosum.

Although in Figs. 1 and 2 the marginal callosum is represented by a single artery, for the purpose of simplifying the global conception of the arterial vessels, it generally consists of two or three branches which are the prefrontal, the internal frontal, and the internal frontal parietal.

enters the artery so that at the moment it reaches 8 or 10 c.e. he can advise the x-ray operator to expose the first plate at that instant. The second exposure is made two seconds later; the third is made two and one-half seconds after the second. In the meantime the assistant places the first and second plates under lead protectors. The plates are removed and sent for development and preparations are made for a second injection of thorotrast should the first injection have proved unsatisfactory and the visibility of the cerebral arteries be incomplete.

As soon as the injection is finished, the needle is removed from the carotid and a wad of gauze is introduced into the bed of the wound. When it is certain that the hemorrhage has been stopped, the edges of the cutaneous incision are sutured. A surgical dressing terminates the operation.

Although it might appear to be a complicated and difficult operation, anyone who carries it out will be convinced that in reality it is not so. We have been able to complete it in a short time and have almost always been obliged to await the development of the plates by the radiologist. The entire procedure, including the time used in the operation and the development and fixation of the films, takes up to about forty minutes.

A point worthy of mention is that in the majority of cases the patients feel no discomfort of any kind, although some complain for a short time of pain in region of the incision and of difficulty in swallowing. As an exception in some cases there is a slight fever, which never exceeds  $38.5^{\circ}$  C. and which seldom lasts more than forty-eight hours.

In regard to possible late disturbances from the thorotrast, I have not had an extended personal experience, and shall cite the assertions of Moniz. He has assured me that, even if the colloidal suspension of thorotrast might remain for a long period in the liver and at times even in the spleen and the bone marrow, it is improbable that it would cause disorders or disturbances of importance to the patients. I believe it is of great interest and importance that a careful and systematized study be made of the biological processes of elimination of the thorotrast in these patients.

In addition there exist certain lesions of the brain whose diagnosis was impossible or imprecise before the advent of this method of exploration. In angiography we have an indisputable method for diagnosing especially the encephalic aneurysms and angiomias, as well as for studying cerebral hemorrhages caused by trauma. Another chapter of neurosurgery of great interest and the study of which would be greatly facilitated by this method is that of the meningeal tumors. Given the curious circumstance that the speed of circulation in the vascular territory of the tumors is slower than in the normal vessels of the brain, we can visualize the tumor in the phlebogram of the second phase, since the blood charged with colloid is still in the capillary phase of the tumor (first phase of phlebogram) and marks its dimensions and edges.



The first phase shows with astonishing regularity a series of vessels distributed in a radiating form, the volume increasing as it approaches the periphery. In normal cases the phlebography of the first phase which, as I have said, is extraordinarily constant, corresponds almost exactly to Fig. 3.

The second phase shows the great venous trunks clearly outlined: the superior longitudinal sinus, describing a curve parallel to the cranial vault; and the veins and ampulla of Galen, occupying the posterior and middle parts of the brain. The ampulla of Galen curves around the splenium and is the principal tributary of the straight sinus. The two veins of Galen which with the basilar vein form the ampulla of Galen come principally from the veins of the hemispheres and the veins of the choroid plexuses of the lateral ventricles.



Fig. 3.—First phase phlebography.

In the phlebograms the positions of the vein of Galen and the superior longitudinal sinus are extraordinarily constant. The lateral sinus is seen quite frequently in union with the posterior part of the vein of Labbé, generally very voluminous, both leading into the torcular Herophili. The inferior lateral sinus continues with a curve of inferior concavity with the straight sinus; the ampulla of Galen and the vein of Galen are between the interior longitudinal sinus and the vein of Labbé.

With this description clarified by the accompanying illustrations, I have described as clearly as possible my conception of the habitual aspect which normal phlebograms present and in the next following shall explain their possible alterations.

#### INTERPRETATION OF ANGIOGRAMS

Among the fundamental changes of position and relationships which are observed in the cerebral vessels as a result of disease and from the

Therefore, the pericallosum and the marginal callosum, both emerging from the anterior cerebral artery, describe a curve and are parallel to each other and at the same time parallel to the cranial vault. The constancy with which cerebral arteries are found in the position just described makes the study of the accompanying illustrations of great importance.



Fig. 1.—Arteriography.

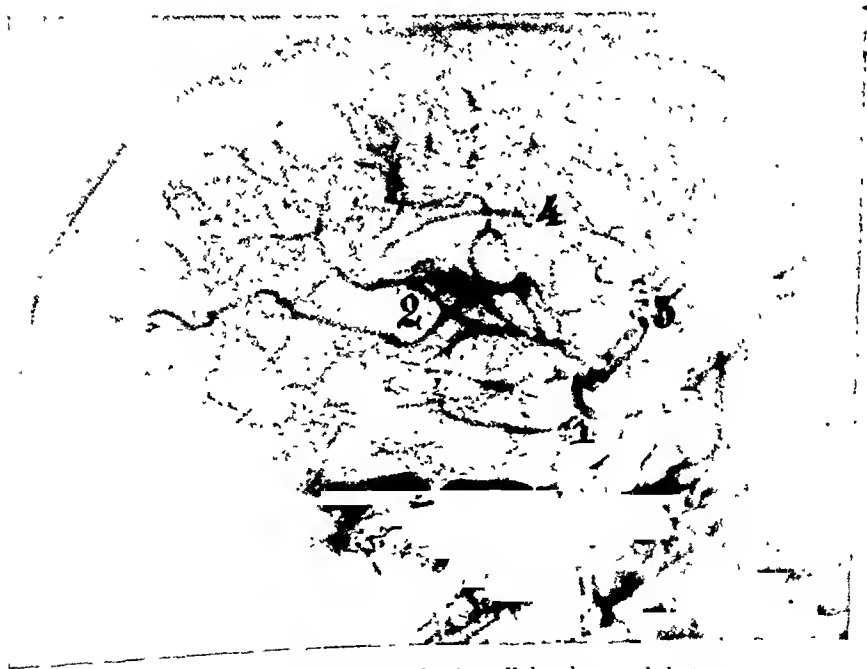


Fig. 2.—Normal arteriography in a living human being.

2. *Cerebral Phlebography.*—In cerebral phlebography two phases are considered; in the first there appear the ascending and descending veins and in the second the large venous trunks.

revealed in the different angiograms and which have been verified in patients by surgical operation or by post-mortem examination.

*Frontal Tumors.*—In this first group I present six arteriograms, obtained in an equal number of cases of frontal lobe tumor. In all of them there is, as a common alteration, deviation of the anterior frontal artery, more or less accented according to the evolution of the growing tumor.

At the same time, there are abnormal modifications of the Sylvian group, which in the most severe cases can have the anterior two-thirds displaced backward and downward. The shape and position of the carotid siphon may also be altered, as can be demonstrated in the first of the cases presented in this group (Fig. 6), where it has been



FIG. 6.—Frontal tumor

reduced to a single semicircular posterior cavity with the disappearance of the whole segment described as the true carotid siphon. Analogously, one can observe how the pericallosum and marginal callosum may be raised, information which would indicate the interhemispherical invasion of the tumor or its bilateralism.

In vascular tumors of this region, in addition to the arterial displacements before described, one can see the shadow produced by the newly formed vessels which irrigate it and which in many cases cross through the capsule. It is not possible generally to know these vessels, which are totally anomalous, from those which come from them, or to know

interpretation of which in the great majority of cases one can localize the lesions, I place in the foreground expanding lesions which, because of their growth, cause displacement and deformities in position and shape of the cerebral vessels. I leave until later the vascular tumors and aneurysms, believing that in these the interpretation of angiograms offers less difficulty. I shall divide my material into various clinical groups determined according to the location of the lesions which are

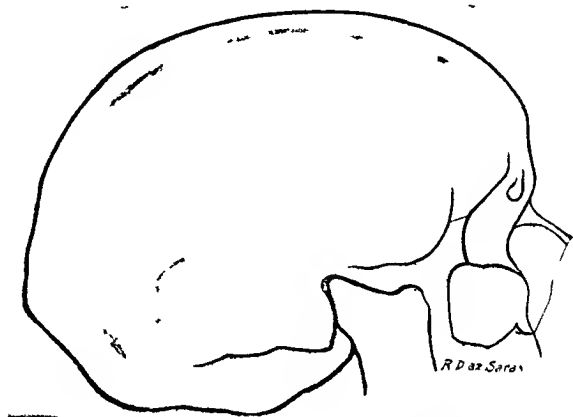


Fig. 4 —Second phase phlebography

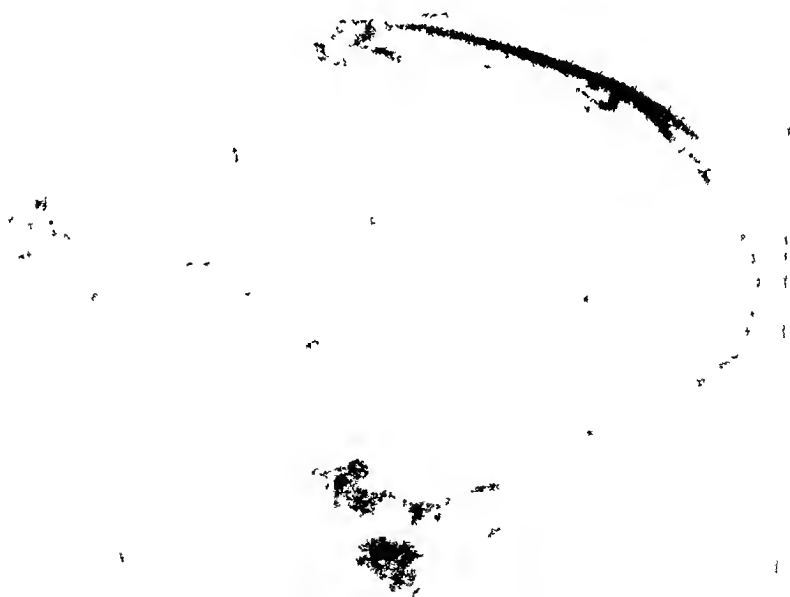


Fig. 5 —Second phase phlebography in a normal living human being.

University of Madrid, is the similarity that can occur in the arteriograms of low temporal lobe tumors and of tumors of the acoustic nerve when the latter are of a sufficient size. The great importance of localization in these cases will be understood when one considers that the surgical approach is totally different in the two instances, since in the first case the trephination will be subtemporal, while in the second it will be suboccipital.

*Posterior Tumors.*—In this group I believe it necessary to make a topographical subdivision, on the one hand the tumors which are in the occipital lobe and on the other hand those which affect the cerebello-pontine angle. When these latter reach a certain size, they push the occipital lobe up and from the arteriographic point of view can give a picture similar to that of occipital lobe tumors.



Fig. 8.—Posterior tumor.

These tumors are localized by the displacement of the posterior third and on occasion of the middle third of the Sylvian group, and it is curious to observe how this arterial group adopts an oblique position which may be very marked, the carotid siphon presenting no modifications in form or dimensions. The pericallosal artery may be seen altered in position in its posterior third and on occasions also in its middle third, in these cases its normal curvature becomes altered until the lower concavity which it normally describes becomes changed almost into a

on which arterial trunk they depend. Phlebograms in frontal tumors often present alterations relative to normal phlebograms.

When the intracranial pressure is very great, the upper and lower lateral sinuses are outlined as being greatly increased in dimension and accented in degree of opaqueness; these alterations are always more marked in the side opposite the tumor.

*Temporal Tumors.*—In this group I present five cases whose common characteristic is the displacement of the Sylvian group, in greater degree the larger the tumor. In addition, the location of the tumefaction will occasion differences of position and forms in the arteriograms. In the cases in which the tumor grows down and toward the middle line, an increase in the volume of the lateral ventricle will result. In some

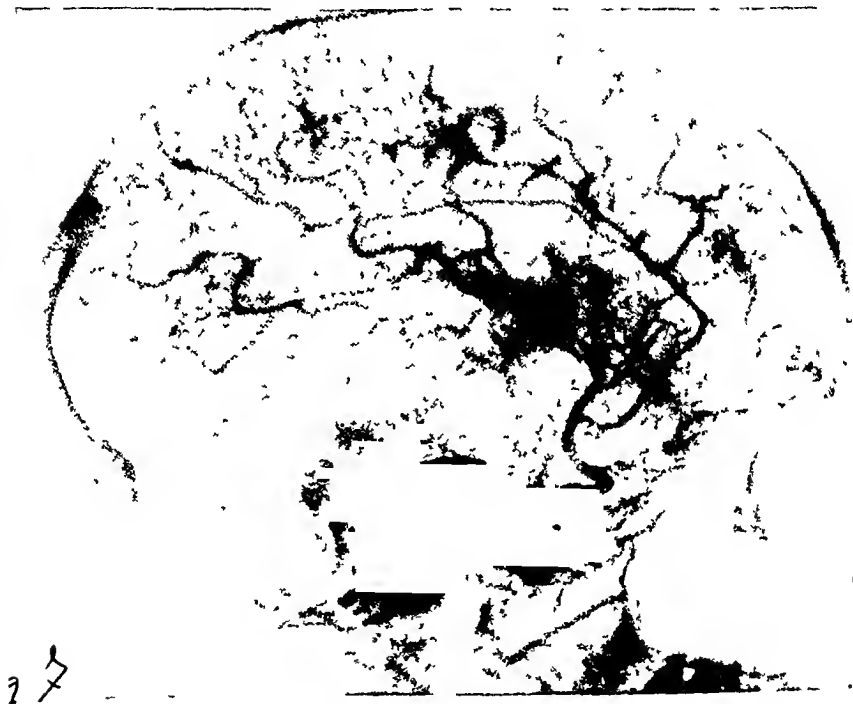


Fig 7—Temporal tumor

cases and at first sight this can mask the tumor since there is presented a diverging separation of the arteries which constitute the Sylvian group, caused by the ventricular dilation. Save in the cases in which the tumor is large, the carotid siphon has its normal conformation; the anterior frontal, pericallosal and marginal callosal arteries are not usually very much altered. Only when the tumor enlarges to the middle line is there any appreciable elevation of the last two arteries of the group cited.

An important consideration, which I shall explain more fully when describing one of the cases studied in the Faculty of Medicine of the

pericallosal and the marginal callosal arteries. Frequently, when the tumor grows slowly, the angiograms show the above arteries, giving a sinuous appearance and designing S-shapes, so typical and which are alone sufficient to show the location of the tumefaction. When, in addition to what has already been described, there is a vascular or meningeal tumor, for example, an angioma, in the very place radiographed, the alterations of form and position of the arteries mentioned and the shadow of the tumor itself are combined. Either alteration by itself would be sufficient to establish a correct diagnosis.

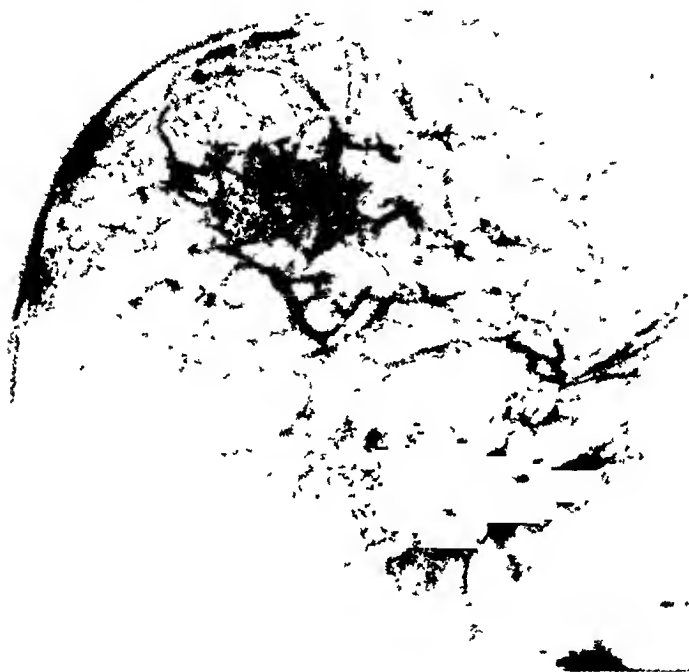


Fig. 10 —Vascular tumor

In the preceding I believe I have described the most important things which can be deduced from the interpretation of the angiograms which confirm observations on the study of cerebral tumors by means of angiography.

I present below two cases of aneurysms, one angioma and two meningeal tumors, whose interpretation I do not believe requires any explanation.

*Aneurysms* —In these cases the arteriographic images usually show no alteration in shape or position of the arteries of the brain save for the vessel in which the tumor is located. Nevertheless, I wish to call attention to the curious tortuosity which all the arteries present in general arteriosclerosis, a fact which I have observed in all the angiograms.

straight line. In spite of the fact that in no instance have I seen its curvature inverted, that is to say, having the concavity upward, and although I do not theoretically deny its possibility, it is convenient, in general to say that the rectilineation of the pericallosum and marginal callosum are caused by occipital tumors, but that the curving in of the upper concavity of these arteries is always produced by tumors of the parietal region, which we shall discuss later.

Phlebography in the study of tumors of the occipital region gives us data of extraordinary value since these tumors, because of their position, usually produce compression of the torcular Herophili and of the lateral sinus, and also in some cases of the straight sinus, which results in the gurgitation of the venous system on the side of the tumor.

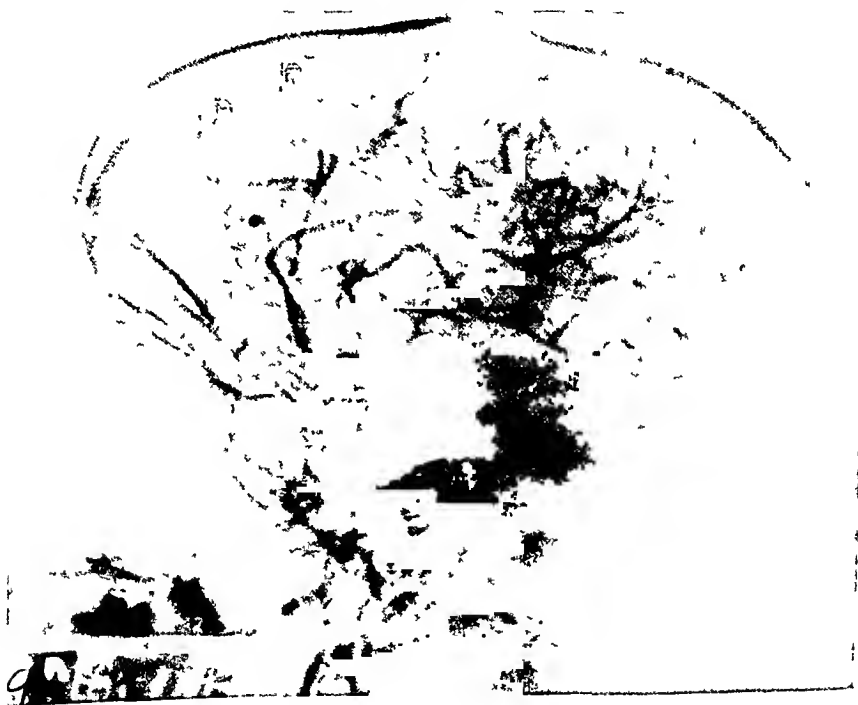


Fig 9 —Parietal tumor

*Parietal Tumors.*—This group of tumors can be diagnosed easily and early, because from the beginning they cause alterations in the vascular system and because, according to Cushing, the parietal region is so frequently the site of meningeal and angiomatous tumors.

In these tumors the carotid siphon preserves its normal position; the ascending frontal and the Sylvian group do not change their relationship. On the contrary, the pericallosum and marginal callosum are usually displaced downward and form a curve with concavity upward, which is just the opposite curve to the one usually described by the



pericallosal and the marginal callosal arteries. Frequently, when the tumor grows slowly, the angiograms show the above arteries, giving a sinuous appearance and designing S-shapes, so typical and which are alone sufficient to show the location of the tumefaction. When, in addition to what has already been described, there is a vascular or meningeal tumor, for example, an angioma, in the very place radiographed, the alterations of form and position of the arteries mentioned and the shadow of the tumor itself are combined. Either alteration by itself would be sufficient to establish a correct diagnosis.

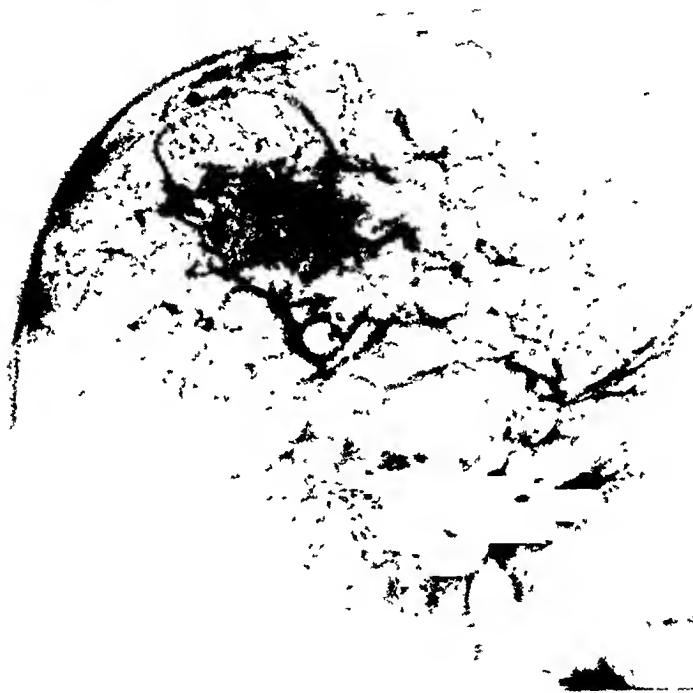


Fig 10 —Vascular tumor.

In the preceding I believe I have described the most important things which can be deduced from the interpretation of the angiograms which confirm observations on the study of cerebral tumors by means of angiography.

I present below two cases of aneurysms, one angioma and two meningeal tumors, whose interpretation I do not believe requires any explanation.

*Aneurysms*—In these cases the arteriographic images usually show no alteration in shape or position of the arteries of the brain save for the vessel in which the tumor is located. Nevertheless, I wish to call attention to the curious tortuosity which all the arteries present in general arteriosclerosis, a fact which I have observed in all the angiograms

in which an aneurysm has been found. The case which I present is that of an aneurysm of the artery of the angular gyrus which gave no cerebral symptomatology; as pathologic antecedents there were tertiary syphilis and a general state of arteriosclerosis.

#### CONCLUSIONS

**ANATOMICAL.**—Concerning the anatomy of the arteries, one is filled with astonishment that those of greatest clinical and anatomical importance are described so inaccurately in the classic and sanctioned books on anatomy. The relationships and the morphologic disposition of the extracranial arteries which the anatomists describe are exact, both in the corpse and the living human being; they are not exact, however, when they refer to the cerebral circulation in the human being, and this can be proved by comparing the data which have been obtained from angiograms with what the most renowned anatomists tell us; thus, we know the exact anatomical descriptions as they refer to the dissection of a corpse, but in contrast angiography shows us the position and reciprocal relations in the arterial vessels of patients; this difference of conformation between the corpse and the living patient has given anatomical data of great interest.

*Carotid Siphon.*—The anatomists tell us that the carotid siphon describes a curve with concavity backward in the cavernous sinus, and after a short horizontal course describes another curve with concavity forward. Indeed, the arteriograms demonstrate that this position is extraordinarily infrequent in a living human being, since there is scarcely one case in 500 in which this is true. From the study of arteriograms, we can describe the morphologic arrangement in the following manner: In the great majority of cases the internal carotid after the horizontal course describes another curve of posterior concavity and on occasion another of anterior concavity; this morphologic arrangement prompts us to call it a double siphon, which is so frequent in arteriograms that it is present in 69 per cent of the cases. In its intracranial path the internal carotid gives the following collaterals: the posterior communicating artery, the anterior choroidal, and the ophthalmic.

*Middle or Sylvian Cerebral Artery.*—This arterial trunk is in the great majority of cases very short. The arteriograms often show the existence of an abnormality which manifests itself by the fact that many branches which usually spring from the Sylvian (posterior parietal and posterior temporal) arteries spring instead from the internal carotid.

*Posterior Cerebral Artery.*—It also springs from the internal carotid in some cases. According to Moniz, this abnormality is almost always unilateral.

*Anterior Cerebral Artery.* This artery which continues with the pericallousum and with the internal frontal parietal must be considered as a collateral of the anterior cerebral artery.

*Marginal Genuate Artery.* Rarely is this artery a single vessel, but generally there are several arteries which irrigate the marginal calcarine fissure.

*Anatomy of the Veins.* The ascending and descending superficial veins as well as the posterior segment of the vein of Labbé open into the lateral sinus or into the torcular Herophili.

The straight sinus ascends, describing an angle of anterior curvature of some 70 to 80 degrees on the plane of the lateral sinus. In phlebogrammas the inferior longitudinal sinus has the appearance of being the continuation of the straight sinus, giving the impression of a curved line of continuous path.

Since all these anatomical data have been revealed by angiogrammas, we are obliged to admit that the description of the vascular relations in books of anatomy are totally different from the morphologic relations that exist in dynamic or vital vascular anatomy, not only in the functional observation of the arteries and veins, but in all the tissues which are maintained in a definite position by their vital activity.

*Physiogrammas.* These constitute the necessary complement of the anatomical material of as much importance clinically and diagnostically as those previously described. The careful study of angiogrammas and serial angiogrammas of the circulation of the head, made by Moritz, Lima and Caldas, who have been able to obtain six radiographs of each side with various time intervals between each one of them, allows us to arrive at the following physiologic conclusions:

1. The speed of the circulation of the blood through the capillary arteries and cerebral veins is two seconds.
2. The speed of the circulation of the blood from the internal carotid artery to the lateral jugular veins is four or more seconds.
3. The speed of the circulation of the blood in the arteriovenous territory from the external carotid to the external jugulars is from five to six seconds.
4. The meningeal circulation is perceptibly the slowest of all those dependent on the external carotid. It is a known and proved phenomenon that pathologic changes considerably alter the cerebral circulation.

*Comments.* Notwithstanding the fact that the above anatomical and physiologic conclusions are of extraordinary scientific and diagnostic interest, they will be of still greater value when they can be proved with more abundant material, inasmuch as they are not only of great practical use to the neurologist, but will be of immediate help to the patient.

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# CARCINOMA OF THE INTRAPANCREATIC PORTION OF THE COMMON BILE DUCT

ALEXANDER BRUNSCHWIG, M.D., AND DWIGHT E. CLARK, M.D.,  
CHICAGO, ILL.

*(From the Departments of Surgery and Medicine, the University of Chicago)*

**I**N CONNECTION with the general interest in the operative treatment of carcinoma of the ampulla of Vater, and of the head of the pancreas, attention may be drawn to the carcinomas which arise from the common duct apart from the ampulla itself. It would appear that such neoplasms are quite rare from the number of cases that have been reported. Stewart, Lieber, and Morgan have recently reviewed the literature on the subject and state that of 86 cases abstracted, 20 were regarded as acceptable on the basis of clinical history, gross and microscopic studies of the primary lesion. Fifteen additional cases, although probably authentic, were not included because of lack of a clinical history or because of insufficient details.

Attempts at surgical removal have been very infrequent since the above-mentioned authors were able to collect records of only 3 such operations. Their summary is included in Table I (first 3 cases). Garlock in 1939 reported a successful resection.

We have had occasion to operate upon 2 patients with carcinoma of the common duct and the purpose of this report is to record these experiences.

CASE 1.—S. T. (Hospital No. 248815), white male, 71 years of age, was admitted to the Medical Service of the University of Chicago Clinics on Sept. 16, 1940, complaining of polydipsia, polyuria, and epigastric distress for eight months, loss of 56 pounds during this period, and jaundice for three months. Urinalysis, sugar +++, acetone +++, diacetic acid +++, albumin, trace; fasting blood sugar, 353 mg. per cent; icteric index, 38; W.B.C., 15,000; R.B.C., 2,800,000.

Following appropriate diabetic management, the patient was considered ready for exploratory operation on Sept. 26, 1940, which procedure was undertaken with the diagnosis of carcinoma of head of pancreas, the icterus not having improved during the period in the hospital. Preoperative blood transfusions were given.

Under novocain spinal anesthesia the abdomen was entered through a high midline incision; a moderate amount of clear yellow fluid escaped. Palpation of the liver, spleen, and peritoneum failed to reveal metastases. The gall bladder was markedly distended, the wall thickened, but no stones were palpated. The common duct was observed to be about the diameter of the thumb and palpation failed to reveal stones. Palpation of the head of the pancreas revealed it to be very firm; the remainder of the pancreas also felt firmer than normal but not as hard as the head. An incision was made into the head for removal of a small bit of tissue for frozen section. This revealed carcinoma. Accordingly, the pylorus was transected and the proximal end invaginated. The head of the pancreas and duodenum were mobilized by incision in the peritoneum along the greater curvature of the latter. The dilated common duct was transected above the duodenum with

The clinical conclusions can be arranged in two groups: (1) the verification of a doubtful clinical diagnosis, or (2) the diagnosis of a lesion that was unsuspected clinically.

From all that has been said, we conclude that the evidence provided by a complete angiographic exploration can establish in many cases an exact diagnosis of a lesion which is impossible to define and to localize by other means of exploration, as in cerebral aneurysm and angioma. The clinician also can be helped to define the exact localization with the data that are deduced from a comparative examination of angiograms. Nevertheless, in some cases angiographic images with normal characteristics are found in patients with obvious lesions that ought to be diagnosed by other means. Because of its harmlessness and the abundance of data which the angiogram gives us, it deserves to be the first test of exploration which is performed on patients whose clinical symptoms are not sufficient to allow an exact diagnosis or localization. In many cases the interpretation of the angiograms can achieve this purpose and it is of such therapeutic importance that in many cases it decides the surgical technique to be followed.

When clinical exploration is insufficient for the diagnosis, one may complement the exploration by other means, as by ventriculography and encephalography; the data deduced from various methods will surely be of unmistakable utility in throwing light on the diagnosis and localization.

We all know that the many new methods of exploration used in foreign clinics must be introduced to current practice, and I hope that the method of exploration which I have described will be received with the benevolence it deserves because of its immediate utility and absolute harmlessness to the patient and because it is a technique accessible to all who have had even an average surgical education.

Still more, I believe it ought to be adopted because it is applicable in many cases which are considered desperate. It opens a new field of hope and can contribute to make the therapeutic successes of neurological surgery greater every day.

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TABLE I  
SUMMARY OF ATTEMPTS AT SURGICAL REMOVAL  
OF CARCINOMA OF COMMON BILE DUCT

YEAR	AUTHOR	OPERATION	RESULT
1902	Uliszewski, Case 1	Resection of gall bladder, cystic duct, and common duct; drainage of hepatic duct	Patient died 3 days after operation
1909	Morian, Case 4	Resection, cholecystoduodenostomy	Patient well 10 mo. after operation
1935	Demel	Resection; subserous cholecystectomy; hepaticoduodenostomy; anastomosis of cut ends of ducts	Patient died 7 mo. after operation
1939	Garlock	Segmental resection of upper common, lower hepatic ducts with inclusion of tumor, cystic duct, and gall bladder; end-to-end anastomosis of common duct	Living and well 10 mo. after operation
1940	Walters, W.	Resection, anastomosis of cut ends	Died 8 days after operation, bronchopneumonia
1940	Brunschwig and Clark, Case 1	Pancreatoduodenectomy, one stage	Patient died 2 days following operation; aspiration pneumonia (?)
1940	Brunschwig and Clark, Case 2	Pancreatoduodenectomy one stage with drainage of transected common duct to exterior	Patient died 3 mo. and 6 days after first operation, 16 days after second operation (peritonitis) performed for anastomosis of gall bladder to jejunum

escape of clear green bile, and doubly ligated with linen thread. Transection of the neck of the pancreas was next performed from above downward. During this step it was discovered that the posterior aspect of the head was firmly adherent to the termination of the superior mesenteric vein and in freeing the former the vein was opened. Ligation of the tear was successful after loss of approximately 100 c.c. of blood and it appeared as though this ligation did not obliterate all of the lumen of the vein. The third portion of the duodenum about 2 to 3 cm. proximal to the ligament of Treitz was transected and the distal end invaginated. The head of the pancreas and practically all of the duodenum were removed. The neck of the pancreas was ligated snugly with linen thread after the main duct was identified and ligated separately. A posterior gastroenterostomy and a cholecystogastrostomy were then performed and the abdomen was closed in layers with a soft rubber drain leading to the site of the head of the pancreas. Silk technique was used throughout.

The patient's immediate postoperative condition was good. He received one transfusion of 600 c.c. citrated blood during the operation and one similar transfusion postoperatively. During the next forty-eight hours the temperature varied between 99.8 and 101° F. rectally, but at noon Sept. 28, 1940, he expired suddenly.

At necropsy there was no peritonitis or evidence of acute pancreatitis nor was there evidence of significant obstruction of the superior mesenteric vein. Two metastatic nodules were found in the upper posterior portions of the liver. The lungs revealed bilateral aspiration pneumonia and purulent bronchitis. Microscopic study of the pancreas revealed almost complete loss of acinar tissue and replacement by fibrous tissue. Many islets were present. There were scattered groups



of carcinoma cells and periductal infiltration by mononuclears and polymorphonuclears. The liver was moderately enlarged and greenish in color. On histologic examination there was slight increase of fibrous tissue and diffuse lymphocytic infiltration in the periportal structures.

The surgical specimen (Fig. 1) consisted of the head of the pancreas and practically all of the duodenum. A probe inserted into the upper cut portion of the common duct passed into the duodenum through a normal ampulla of Vater. Some resistance was encountered proximal to the ampulla. When the common duct was opened, it was found to be constricted by an oval raised plaque on posterior aspect measuring 1.7 cm. in length and 4 mm. in width. This firm plaque exhibited raised rolled edges and its deeper portions were continuous with firm grayish tissue that extended into the adjacent portion of the pancreas. When the head of the pancreas was bisected in several planes, it became obvious that the grayish firm tissue represented neoplastic infiltration. The pancreatic tissue did not appear normal but was dull, yellowish, and mottled. The common duct was quite narrow over the 1.5 cm. course below the plaque and extending to the ampulla. The lining of the common duct was elsewhere negative. The main pancreatic duct was empty and its lumen patent and lining normal in appearance. It emptied separately into the duodenum in the ampulla of Vater.



FIG. 1.—Case 1. Excised head of pancreas, duodenum folded under specimen. C, Opened common bile duct showing raised plaque (T), a carcinoma arising from posterior wall. A block of tissue has been removed from the center of the lesion for microscopic study. The dense fibrotic and abnormal appearance of the pancreatic tissue is due to chronic interstitial pancreatitis and diffuse infiltration of carcinoma from primary site in common duct.

Microscopic study of a section through the plaque in the common duct, cut transversely to the long axis of the latter (Figs. 2A and B), revealed it to be composed of dense cords of large anaplastic carcinoma cells appearing to stream downward into the surrounding pancreas. Sections through the contiguous portion of pancreas showed scattered islands of tumor tissue, islets, and large groups of cancer cells with wide bands of edematous fibrous tissue infiltrated by mononuclears and polymorphs.

*Surgical Pathologic Diagnosis:* Carcinoma of lower segment of common duct with invasion of pancreas; chronic interstitial pancreatitis (obstructive?).

CASE 2.—A. V. (Hospital No. 248811), white, married female, 51 years of age, was admitted to the Surgical Service of the University of Chicago Clinics Sept. 15, 1940. In February, 1940, icterus developed and in March, 1940, a cholecystostomy was performed in another hospital, there being no stones discovered in the

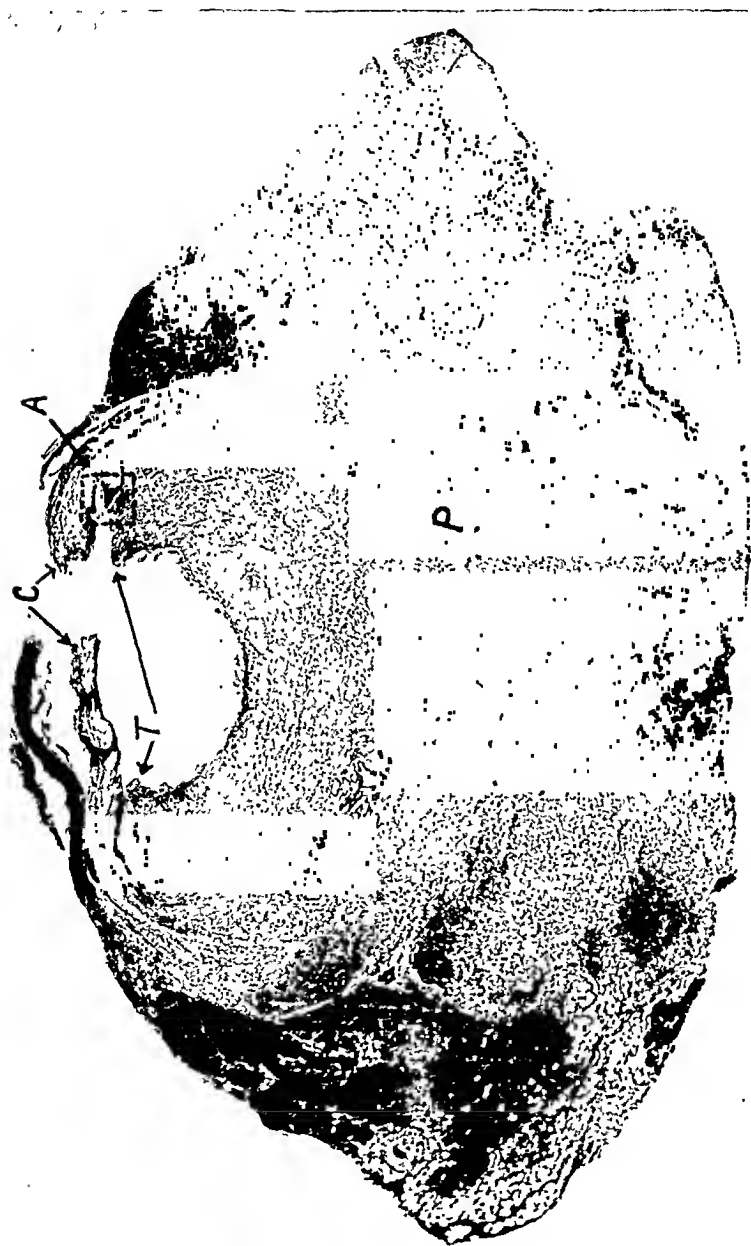


Fig. 2A.—Photomicrograph (X15) of section from gross specimen shown in Fig. 1. The section is in plane transverse to long axis of common duct showing T, raised plaque due to carcinoma which has infiltrated and to a large extent disintegrated the subjacent wall of the common duct. C, Uninvolved portion of common duct. P, Invasion of pancreas by carcinoma. A, Area magnified in Fig. 2B.

gall bladder. The surgeon had noted a small firm mass in the head of the pancreas which was assumed to be a carcinoma. Bile drained continuously from the cholecystostomy wound until one week prior to this admission when the drainage ceased, chills and fever were experienced, and the return of jaundice was noted. W.B.C., 17,500; R.B.C., 3,900,000. Urinalysis, bile ++++; icteric index, 76. Temperature 98° F. Probing of cholecystostomy wound resulted in no discharge of bile. Since cholecystostomy the patient had gained weight and there was no clinical evidence of metastases. She had been quite active in household duties.

Exploratory operation was performed on Sept. 19, 1940, under ethylene ether anesthesia. The abdomen was negative except for adhesions in the upper right quadrant among which was a moderately distended gall bladder whose fundus was adherent to the peritoneal aspect of the previous cholecystostomy wound. The adhesions were cut, the liver palpated and found to be free of metastatic nodules. In the head of the pancreas a very firm nodule was palpated and assumed to be a carcinoma. Accordingly the pylorus was transected and upper segment invaginated, the duodenum and head of pancreas mobilized by incision of peritoneum along the curvature of the second portion of duodenum. The dilated common duct whose walls were thickened was transected about 2 cm. above the duodenum with escape of clear green bile. A probe inserted into the lower segment encountered

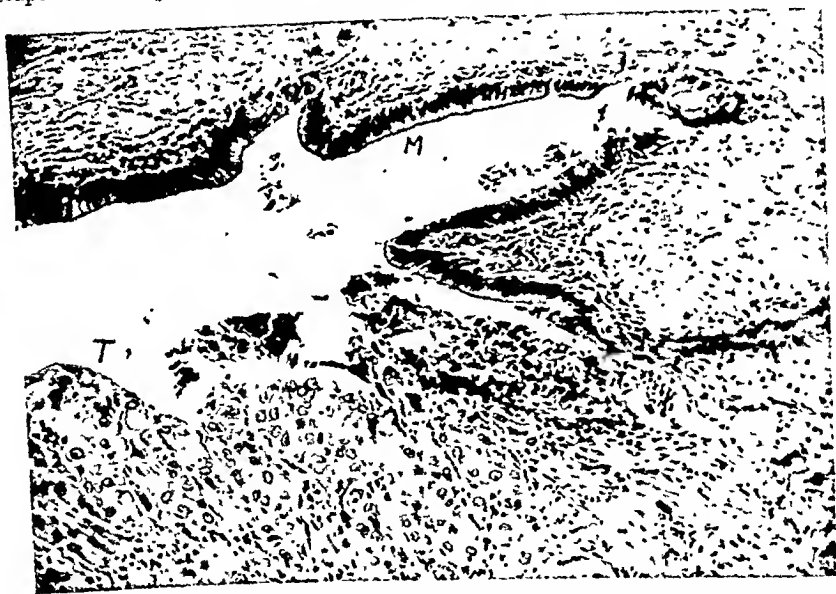


Fig. 2B —Photomicrograph ( $\times 230$ ) of area 1 indicated in Fig. 2A from edge of carcinoma arising in common duct. T. Carcinoma composed of large polyhedral cells tending to form tubules. M. Normal mucosa from uninvolved portion of common duct.

resistance within the head of the pancreas. The neck of the pancreas was transected, the main pancreatic duct identified and ligated, and a silk ligature passed snugly about the whole pancreatic stump. The third portion of the duodenum was transected a short distance proximal to the ligament of Treitz and the distal segment invaginated. The head of the pancreas and practically all the duodenum were removed. Because of the adhesions about the porta hepatis the upper segment of common duct was quite immobile and because it was desired to make this procedure as brief as possible, no anastomosis was attempted between biliary tract and bowel and instead a urethral catheter, No. 24 French, was inserted into the common duct and out through a stab wound in the abdominal wall near the old

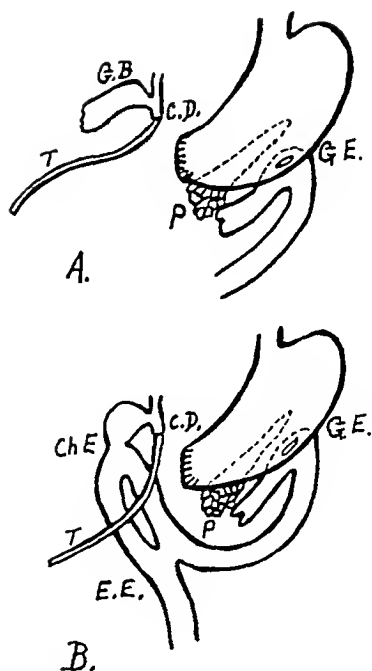


Fig. 3.—A. Diagram of operation performed in Case 2, first stage. The head of the pancreas and duodenum have been removed. The pyloric portion of stomach has been invaginated as has the third portion of the duodenum. The neck of the pancreas (*P*) has been transected. A posterior gastroenterostomy (*G.E.*) has been performed and the common duct (*C.D.*) cannulated to the outside by tube *T*. The gall bladder (*G.B.*) showed a healed cholecystostomy wound in the fundus. B. Diagram of second stage performed 86 days after first stage. A loop of jejunum was brought through the transverse mesocolon for cholecystenterostomy (*Ch.E.*) and below this, enteroenterostomy (*E.E.*). The common duct (*C.D.*) with cannulated tube *T* was not disturbed as it was felt that the latter could be removed subsequently after internal biliary drainage might once be established.

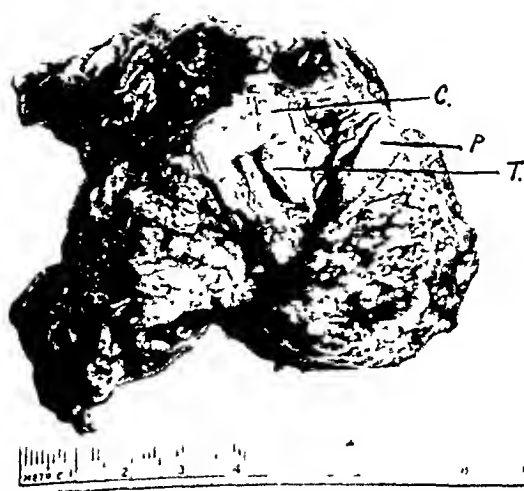


Fig. 1.—Case 2. Excised head of pancreas; the duodenum is folded under the specimen. The common bile duct (*O*) has been opened exposing carcinoma (*T*) bulging into its lumen. *P*. Pancreatic duct, also laid open.

cholecystostomy opening (Fig. 3). The abdomen was closed in layers, a soft rubber drain being inserted into the site of the head of the pancreas.

In surgical pathologic examination of the head of the pancreas and duodenum (Fig. 4), the ampulla of Vater was identified and found to be normal. The small firm tumor palpated within the head of the pancreas, when exposed by incision through the latter, proved to be a rounded mass 1.5 by 1 by 1 cm. arising in and constricting markedly the common duct at about 1.5 cm. above the ampulla. Slight infiltration of the surrounding pancreatic tissue was noted. When the common duct was opened, the grayish mass was seen bulging into the lumen or its anterior aspect. The pancreatic tissue appeared otherwise normal and the main pancreatic duct was laid open and found to be empty.

Microscopic sections through the mass and common duct wall (Fig. 5) showed the former to be composed of small, very anaplastic rounded and polyhedral malignant cells, arranged in dense masses and cords. The cells showed extreme anaplasia. The common duct above the tumor showed thickening of the wall due to fibrosis, and diffuse leucocytic infiltration. Sections through pancreatic tissue away from the tumor showed essentially normal pancreas except for some edema in the outer acinar tissue.

*Surgical Pathologic Diagnosis:* Carcinoma of the common duct, arising from that portion coursing through the head of the pancreas.

The postoperative course was essentially uneventful except that bile did not drain freely from the tube leading into the common duct. Indeed the icteric index rose to 137 on the eighteenth postoperative day, but by the seventy-eighth day it had finally fallen to 9.3. During the postoperative period the patient became visibly emaciated and the biliary drainage which varied from 150 to 1,000 c.c. a day was for a time instilled in 400 c.c. daily doses into the stomach by means of a Levine tube. This procedure was discontinued because it nauseated the patient. Vitamins A, B, B<sub>2</sub>, C, and D were administered daily by mouth as well as 0.2 Gm. of nicotinic acid, vitamin K, and 1.8 Gm. of bile salts. The appetite varied and on occasions was quite good. There was no steatorrhea. For a brief period there was a mucoid bile-tinged discharge from the sinus through which the soft rubber drain had been inserted into the pancreatic stump. The slight discharge from this caused considerable erythema and superficial maceration of the surrounding skin. The latter was finally controlled by aluminum paste applications. The patient's weight prior to operation was 42.3 kg. It fell to 29.9 kg. on the sixty-first day, but rose slightly to 34.5 kg. on the eightieth day at which time she was sitting up out of bed and walking a few steps. On the eighty-second day, the abdominal incision being well healed, another laparotomy was performed, the purpose of which was to re-establish continuity between the biliary tract and intestines (Fig. 3B). The previous upper midline incision scar was excised and the upper peritoneal cavity entered. There were many fibrous adhesions. The fundus of the gall bladder was freed from adherence to the old cholecystostomy scar. A loop of jejunum about 12 inches below the gastroenterostomy was then brought up through the mesocolon for cholecystoenterostomy. About 6 inches below this an enteroenterostomy was performed between afferent and efferent loops of jejunum. The liver, exposed at various points, appeared normal. The abdomen was closed in layers. Silk technique was used throughout. During this procedure the catheter in the stump of the common duct was left undisturbed, a clamp being applied just above the skin level. The immediate postoperative condition was good, the maximum temperature being 99.8° F. on the second day. The temperature was normal until the eighth day when it rose to 101° F. The upper portion of the wound separated with discharge of upper bowel contents and bile. The patient's general condition, however, remained fair except for temperature up to 100.6° F. until the sixteenth day after the second operation, which was the ninety-sixth day after the first procedure, when general collapse and death ensued.

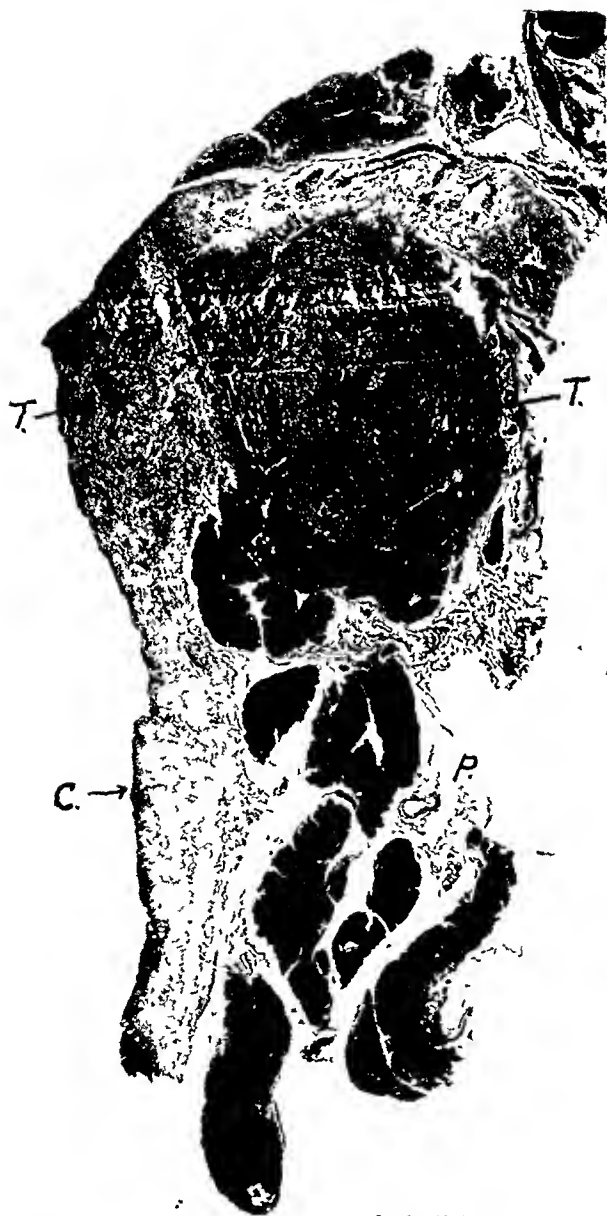


FIG. 5A.—Photomicrograph (X8) of longitudinal section through common duct carcinoma shown in Fig. 1. This section passes through a plane showing maximum extent of invasion of tumor (T), into surrounding pancreatic tissue, and does not include plane of maximum extent of origin from common duct (C). P Uninvolved pancreas.

*Necropsy:* Generalized fibrinopurulent peritonitis (old). There was about 1 cm. separation at the right angle of the cholecystenterostomy, which opening communicated with the gaping upper portion of the abdominal incision. Patent sinus tract from the transected common, also leading to the abdominal wound. No gross or microscopic evidence of carcinoma anywhere in the body. No significant fatty infiltration or degeneration in the liver; diffuse periportal lymphocytic infiltration and slight fibroplasia in periportal septa.

#### DISCUSSION

It is obvious that a specific preoperative diagnosis of carcinoma of the common bile duct can hardly be made with available methods of clinical study. The general clinical picture present in such cases is also consistent with that of a neoplasm of the ampulla of Vater, head of the pancreas, gall bladder with invasion of the common duct, and also of the hepatic ducts. In both the patients described above the clinical diagnosis of cancer of the head of the pancreas or ampulla was made and as a result of palpation at laparotomy it was thought the former diagnosis was confirmed. The operative procedures for excision of such neoplasms were followed. The true situation was discovered only upon study of the surgical specimens in the laboratory.

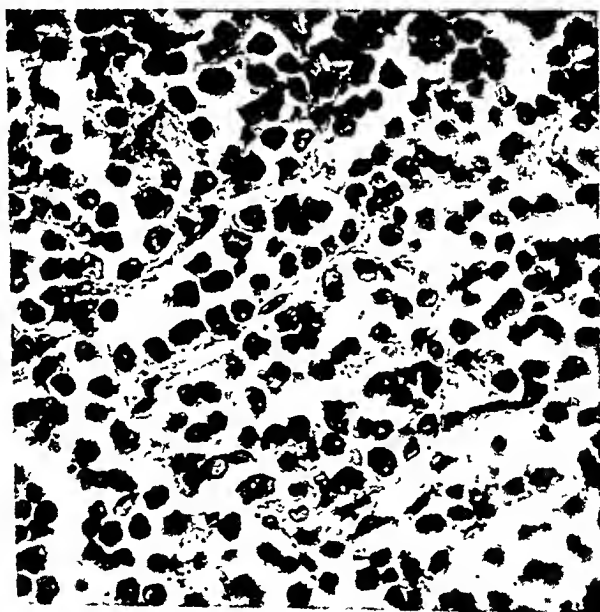


Fig. 5B.—Photomicrograph ( $\times 625$ ) of section of tumor shown in Fig. 5A. The diagnosis of carcinoma was made. The cells show extreme anaplasia.

In one of the patients the disease was extensive; in the second case, in spite of the long history, the process was still localized. Because of the rarity of small localized malignant tumors arising from the intra-pancreatic portion of the common duct this condition was not even considered at the time of operation. In retrospect, it might have been

possible to excise the *second neoplasm* by a more conservative procedure (segmented resection and anastomosis over a T-tube). It would appear that this possibility should be borne in mind when encountering small tumor masses buried in the head of the pancreas near the course of the common duct. Incision into the pancreas for biopsy or incidental to exposure of the lower segment of common duct would not, in light of experience in recent years, be fraught with great danger of inducing acute pancreatitis.

Another instance of slowly growing carcinomas of the common duct is the case cited by Walters and Snell. The tumor arose from the supraduodenal segment; a cholecystoenterostomy had been performed and there was survival for four years. These authors cite the records of seven patients with common duct cancer treated by cholecystoenterostomy only and with an average survival of twenty months.

### CONCLUSIONS

1. Carcinoma of the lower segment of the common bile duct appears to be rare, although with the present interest in excision of tumors in this region their incidence may be found to be greater than hitherto suspected.

2. The clinical picture does not differ sufficiently from that afforded by cancer of the ampulla, confluence of the extrahepatic bile and cystic ducts, cancer of the cystic duct or gall bladder, of the ampulla of Vater or of the head of the pancreas to permit of specific preoperative diagnosis. However, such a possibility should be considered when on palpation small tumor masses are felt in the head of the pancreas in the course of the common duct.

3. Attempts at excision are justifiable in the absence of evidence of metastases since, as a group, they are not rapidly growing tumors and metastasize relatively late.

The procedures indicated are pancreatoduodenectomy when the pancreas is involved (as for carcinoma of the head of the pancreas); however, a more conservative segmental resection may be possible where the tumors are still quite small.

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# A METHOD FOR THE COLLECTION OF THE ENTIRE BILE OUTPUT IN HUMAN PATIENTS WITH CHOLEDOCHOSTOMY TUBES

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THE study of physiology of the liver as related to the secretion of bile has been impaired by lack of a satisfactory method for collecting the entire biliary output in human subjects. Kocour and Ivy<sup>4</sup> have devised a satisfactory method for complete collection of bile in animals by means of ligation of the common bile duct and application of suction to an intraductal cannula. Such procedures are not applicable to human subjects. When a spontaneous complete biliary fistula does occur, moreover, there is almost always coexistent liver damage as a result of the underlying disease.

It has been shown that the sphincter of Oddi exerts a definite resistance to the flow of fluid from the common bile duct into the duodenum in human patients with choledochostomy tubes.<sup>1-3, 5</sup> It seems reasonable to expect, therefore, that application of suction to a choledochostomy tube would create a channel of less resistance than the normal channel with its sphincter mechanism and would establish a complete external biliary fistula. Making use of these principles we have developed a technique for the collection of the total bile output in patients with choledochostomy tubes, and it has proved to be so satisfactory that we wish to present it as a method which will permit the extension of studies of the physiology of the liver in man.

## METHOD

After a series of preliminary observations we learned that most patients with T-tubes inserted into the common bile duct are suitable subjects for application of this technique, but that patients with bile duct intubation with straight catheters of the Nèlaton type do not give consistently satisfactory results.

The negative pressure is applied by means of the apparatus shown in Fig. 1. The source of the suction may be any one of several types of pumps. We used a water-jet type of filter pump. The entire apparatus is sterilized in the autoclave before use, and aseptic technique is used throughout the period of collection. Replacement receptacles are also sterilized before use.

The suction is maintained at a constant level of 12 cm. of water below atmospheric pressure by means of a water valve (Fig. 1 C) which per-

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mits air to enter the system through the open tube in Bottle C if the negative pressure exceeds the hydrostatic pressure exerted by the column of liquid. If the suction source is adjusted so that there is a slow steady entrance of gas bubbles through the open tube, a constant negative pressure is assured.

A double collection system is used. This permits an alternation of the receptacles at four-hour intervals (or in any other manner that is desired) without the slightest interruption of the suction. When the bile is collected in Receptacle A, Tubes  $b_1$ ,  $b_2$ , and  $b_3$  are clamped. At

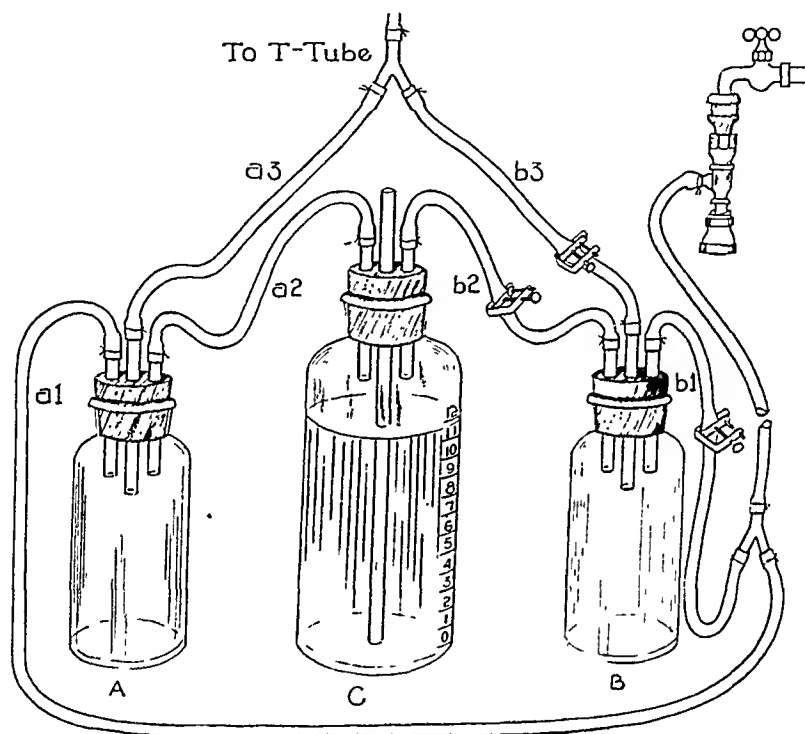


Fig. 1.—Apparatus for application of constant suction to choledochostomy tube. A and B are receptacles for collection of bile; C is a water valve for regulation of pressure.

the end of the collection period before disconnecting Bottle A the clamps are removed from the tubes leading to Receptacle B and are placed on Tubes  $a_1$ ,  $a_2$ , and  $a_3$ . It is essential that there are no kinks in the tubing, no leaks in the connections, no interruption of the suction at its source, and that water in the valve is maintained at the proper level, the loss by evaporation being replaced.

#### PROOF OF METHOD

To be satisfactory the method must produce a practically complete deviation of bile flow, and the success of the method can be determined by examining the feces for biliary constituents. Of these, bile pigment

is the one which is measured most readily by use of existing clinical laboratory facilities. We have used the quantitative urobilinogen test of Watson<sup>6</sup> to determine the presence or absence of bile from the gastrointestinal tract.

Six patients who previously had undergone cholecystectomy, choledochotomy, and intubation of the common bile duct served as subjects for this study. The suction was applied to the T-tube for from four to five days before the stool collection was started, in order to permit evacuation of the intestinal content already containing bile. Intestinal activity was stimulated by the administration of laxatives and enemas during the preparatory period. Finally all stools passed during a four-day period were collected and analyzed for urobilinogen content. During the period of the experiments the patients received the standard hospital diet and neither bile salts nor other biliary constituents, except fluid and electrolytes, were replaced. The Quick prothrombin time, the icterus index, the blood urea nitrogen, the carbon-dioxide combining power, and the plasma chlorides remained normal throughout the duration of the experiment.

The analyses indicated that the deviation of the bile was practically complete in five of the six patients, and in the sixth there was only a small loss of bile into the intestine. The amounts of urobilinogen found in the feces are shown in Table I. In five of the six patients there were 5.88 mg. per day or less, and any value of 5 mg. or less represents practically a complete exclusion of bile from the intestine.

TABLE I  
VALUES OF UROBILINOGEN IN FECES IN PATIENTS WITH SUCTION APPLIED TO  
(CHOLEDOCHOSTOMY TUBES)

PATIENT	MG. OF UROBILINO- GEN PER DAY IN THE FECES	24-HOUR BILE VOLUMES ON SUCCESSIVE DAYS			
		1	2	3	4
1	3.2	370	392	441	376
2	12.15	193	227	208	225
3	1.9	559	594	565	638
4	5.88	378	421	288	439
5	2.08	588	669	577	575
6	1.58	637	647	581	492

\*The low levels of urobilinogen indicate that this technique produces practically complete deviation of the bile. The volumes of the bile aspirated through the tubes are shown also.

#### CONCLUSION

A technique has been developed for the production of "complete" biliary fistulas in human patients with choledochostomy tubes. The method has proved to be satisfactory and makes possible the extension of studies of hepatic physiology in man.

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# HYPERTROPHY OF THE SPHINCTER CHOLEDOCHUS

## A CAUSE OF INTERNAL BILIARY FISTULA

EDWARD A. BOYDEN, PH.D. (MED. SC.), MINNEAPOLIS, MINN.

(From the Department of Anatomy, University of Minnesota)

**I**N ACCORDANCE with the suggestion made in a previous issue of this JOURNAL,<sup>1</sup> namely that an adequate understanding of the pathologic physiology of the choledochoduodenal junction can be obtained only through correlation of clinical and microscopic observations, the following analysis of a unique specimen is herewith presented.

The case in question was called to my attention by Dr. John F. Noble, of the Department of Pathology. At an autopsy of a woman 74 years old, he found three enormous gallstones, the largest measuring approximately 40 mm. in diameter, impacted in the lower end of the common bile duct (Fig. 1). Not only had these distended the duct to almost the size of the duodenum, but the lowest one had telescoped the major papilla until it protruded into the lumen of the gut for a length of 3.5 cm. At its greatest diameter this giant papilla measured 2.5 by 1.6 cm. In this process its upper (basal) end had eventually overlapped the minor papilla by a distance of 15 mm., and the usual slit-like fenestra through which the ducts enter the duodenal wall had been enlarged to a round "window" 3.2 cm. in diameter. Finally, the roof of the papilla had developed a small fistula which eventually would have permitted expulsion of the stones into the lumen of the gut and the production of a gallstone ileus.

As this phenomenon was of special interest to the radiologists, the specimen was photographed and drawn under the direction of Dr. Leo G. Rigler in preparation for a discussion of this aspect of the case. (See Fig. 2 of the article by Rigler, Borman, and Noble.<sup>2</sup>)

The problem which presented itself to the anatomist was the reaction of the musculature of the papilla to the pressure of the terminal stone; that is, which of the circular bands of the sphincter of Oddi (Fig. 2) prevented expulsion of the growing stone through the natural orifice of the papilla? To this end, the pancreatic duct was first dissected, then the terminal 3.5 cm. of the papilla was sectioned serially, at 8 $\mu$ , and stained for smooth muscle with the Mallory-Azon technique.

Attention was first directed to the fate of the main pancreatic duct. Grossly it could be probed through the posterior wall of the papilla to within 3.3 mm. of the orifice of the papilla (see where solid outlines of the ductus pancreaticus end in Fig. 1B). This is approximately the level of the microscopic section shown in Fig. 3A. The lumen of the pancreatic duct still shows in this section, but below this level the duct

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Attention was first directed to the fate of the main pancreatic duct. Grossly it could be probed through the posterior wall of the papilla to within 3.3 mm. of the orifice of the papilla (see where solid outlines of the ductus pancreaticus end in Fig. 1B). This is approximately the level of the microscopic section shown in Fig. 3A. The lumen of the pancreatic duct still shows in this section, but below this level the duct

is represented only by a mass of somewhat macerated glands. The continuities of this mass permit two interpretations: the duct either could have emptied into the valvula-lined cavity interpreted as ampulla (at the level indicated in Fig. 3B) or could have continued to a separate orifice on the posterior end of the papilla (in which case there would have been no ampulla). In either event the terminal portion of the pancreatic duct was occluded, presumably by pressure of the lowest of the three stones. Microscopic sections of the body of the pancreas (prepared by the pathologists) showed "nothing of note." Therefore, the pancreatic juice must have found an outlet through the accessory pancreatic duct and minor papilla, the latter being located at the junction of the major papilla and the anterior wall of the duodenum, 15 mm. below the upper end of the major papilla.

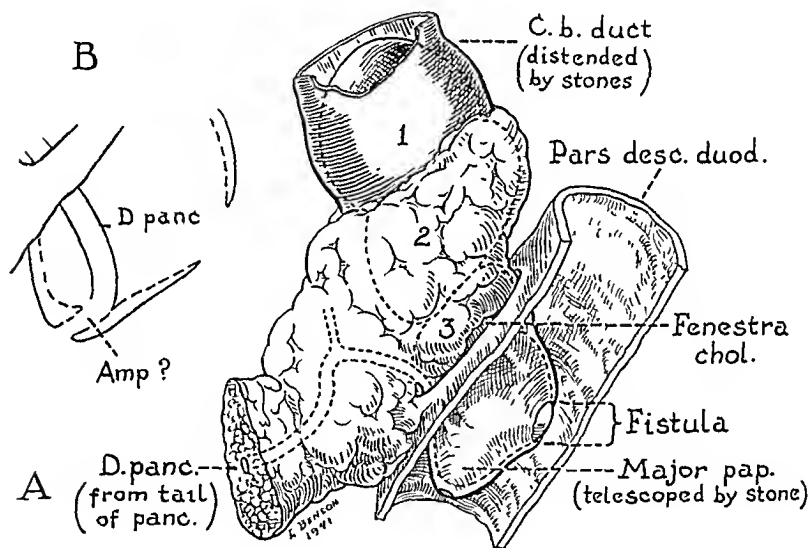


Fig. 1.—A. Dissection of duodenum, pancreas, and bile duct of a woman 71 years old, as seen from the posterior aspect ( $\times 25$ ). Autopsy No. A40-2308 (U. of Minn. Path. Coll.). 1, 2, 3. Gallstones impacted in lower end of common bile duct. *Fenestra chol.* Distended "window" through which ducts enter the duodenum. B. Enlarged detail of major papilla. Pancreatic duct swings across posterior wall of papilla. Its lumen ends where solid outline stops.

Having established the position of the pancreatic duct, it was then possible to identify the sphincter choledochus. This immediately surrounds the common duct and, on the pancreatic side, intervenes between bile and pancreatic ducts. In this specimen (Figs. 3A and B) the left half of the ring was hypertrophied and was the muscle which was holding the stone and preventing its expulsion. The right portion of the ring surrounding the valvula-lined cavity (labeled *Amp.?* in Fig. 3B) was only slightly developed.

Thus it is apparent that in this patient the muscle which was preventing the expulsion of the stone was the sphincter choledochus, this,



regardless of whether the sections are to be interpreted as indicating that the ducts emptied separately or through a common ampulla.

Of special interest are certain facts brought out in the long autopsy report. The patient was hospitalized three times within a period covering the eighteen months before death. The first admission was preceded by a general malaise of ten days' duration, characterized by sharp pain in the upper quadrants, nausea, vomiting, anorexia, and

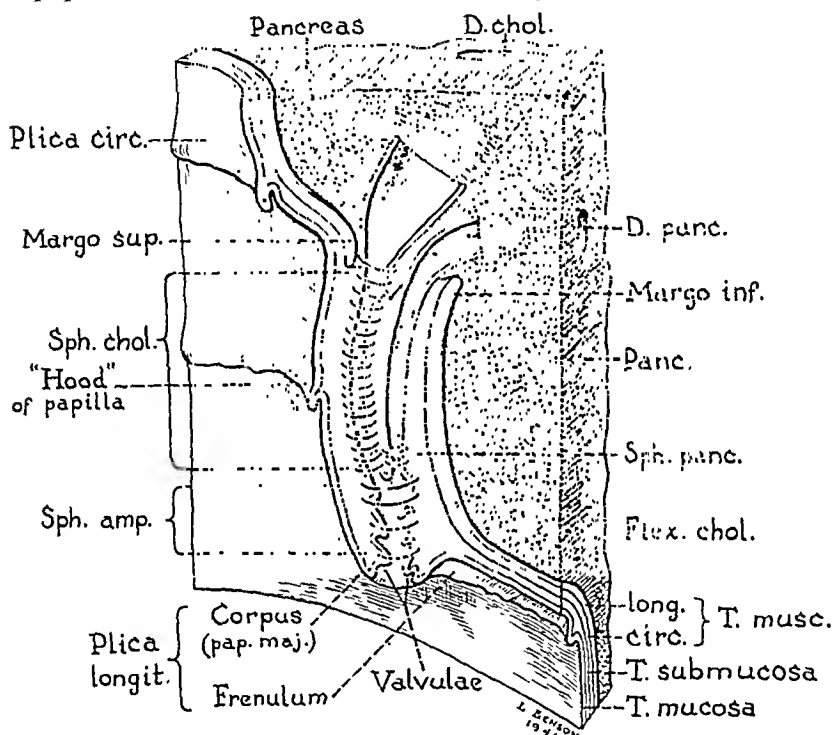


Fig. 2.—Diagram (based on dissected specimen) of a longitudinal section of a normal major papilla, as viewed from the anterior aspect ( $\times 3$ ). This displays the three sets of circular muscles comprising the sphincter of Oddi, which surround the intraduodenal portion of the ducts. *Sph. chol.* Circular sheath around the bile duct (always present). *Sph. amp.* Sheath encircling the ampulla of Vater (well developed in only one-sixth of individuals). *Sph. panc.* Pancreatic sheath (present in only one-third of individuals; cf. Kreilkamp and Boyden, 1910<sup>2</sup>). *Margo sup.* and *inf.* Margins of slitlike windows through which ducts enter the duodenal wall.

jaundice, with stools negative. After three weeks of rest and fat-free diet, resulting in marked improvement and the disappearance of the jaundice, the patient was discharged, the inference being that common duct stones had been passed.

Six months later she was readmitted following an automobile accident. During the five-day period in which she was under observation, examination of the abdomen was negative.

In another eleven months she was admitted again, this time in comatose condition (after severe pain of only two days' duration). Seven hours later the patient expired. Autopsy resulted in a diagnosis of

choledocholithiasis, biliary cirrhosis (involving liver cells around central veins, and dilation of pigment filled intrahepatic ducts), and obstructive jaundice. The gastrointestinal contents were still dark, indicating that some bile still trickled through the papilla, presumably through the channel indicated by the arrow in Fig. 3.1. Had the stones been passed through the fistula, gallstone ileus would surely have resulted.<sup>2</sup>

From the data, it is not possible to estimate how long it took to form these large stones. But in view of the case described by Cameron,<sup>4</sup> in which thirty-eight cholesterol stones (the largest measuring 17 by 15 by 12 mm.) were formed in the eighty-six days elapsing between

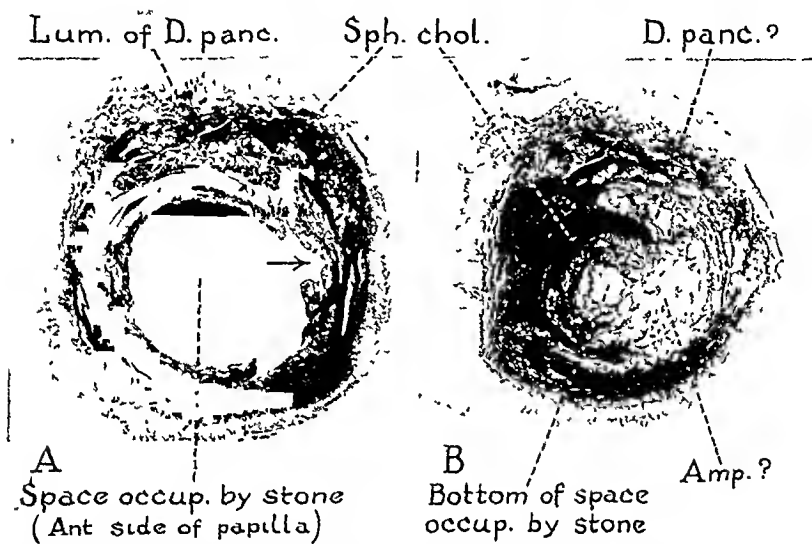


Fig. 3—Two sections through the lower end of the major papilla shown in Fig. 1 ( $\times 5$ ). A, Section  $3\frac{1}{4}$  mm from orifice of papilla, at level where lumen of pancreatic duct stops. Arrow indicates channel to right side of stone for passage of bile. B, Section 0.5 mm below A, at level of bottom of stone (cf Fig. 1B). Amp. ? Either the ampulla (at about level where the pancreatic duct would join it if its lumen had not become obliterated) or the lower end of the bile duct. Note dense hypertrophied ring of the sphincter choledochus, surrounding lower end of cavity occupied by stone.

cholecystostomy and cholecystectomy, it is not unreasonable to assume that the three stones of the specimen in question formed within the eleven months elapsing between the patient's second and third periods of hospitalization.

In reconstructing the sequence of events, it is presumed that a moderate-sized stone which was too large to be passed at once reached the lower end of the papilla and was held by a spasm of the sphincter choledochus. As the stone grew by accretion, the sphincter correspondingly hypertrophied. As more material was added to the upper end of the stone, it extended through the window in the intestinal wall; but being held by other stones in its rear, it simultaneously telescoped the

papilla, drawing the mucosa of the gut out upon it. Finally, it eroded the roof of the papilla, but before it could escape, death from liver damage intervened.

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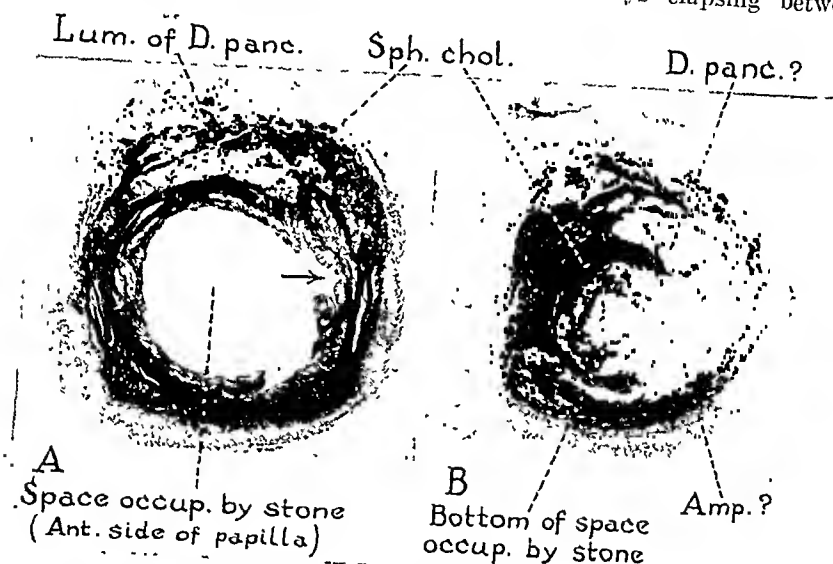


Fig. 3.—Two sections through the lower end of the major papilla shown in Fig. 1 (X5). A, Section 3½ mm. from orifice of papilla, at level where lumen of pancreatic duct stops. Arrow indicates channel to right side of stone for passage of bile. B, Section 0.5 mm. below A, at level of bottom of stone (cf. Fig. 1B). Amp., either the ampulla (at about level where the pancreatic duct would join it if its lumen had not become obliterated) or the lower end of the bile duct. Note dense hypertrophied ring of the sphincter choledochus, surrounding lower end of cavity occupied by stone.

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# COMPARATIVE ABSORPTION RATE OF SULFANILAMIDE FROM THE PLEURAL CAVITY, PERITONEAL CAVITY, AND GASTROINTESTINAL TRACT IN DOGS

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College of Virginia)*

THAT THE sulfonamides may be absorbed when used locally has been reported by several clinical observers.<sup>1-6</sup> For instance, Jensen, Johnsrud, and Nelson<sup>1</sup> have reported that after dusting 10 Gm. of sulfanilamide into a compound fracture site in man, a peak blood concentration of 14 mg. per 100 c.c. was reached after eighteen hours; sixty hours were required for its complete disappearance from the blood. In discussing the local application of sulfanilamide in the clinical treatment of empyema and lung abscess, Adams<sup>2</sup> states: "The blood level of sulfanilamide has been determined at regular intervals, since it is conceivable that absorption to a toxic degree could take place. In our cases, only low levels of sulfanilamide were found." However, no experimental studies concerned with the comparative extent of absorption of sulfanilamide from local application and from the gastrointestinal tract have come to our attention. The obvious importance of this prompted the experiments herein reported in which dogs were used as experimental animals.

Because of the interest of our surgical department in the use of sulfanilamide in the chest cavity and in the peritoneal cavity, absorption from these two sites was compared with absorption from the gastrointestinal tract. The surgical procedures were carried out aseptically under ether anesthesia without premedication. In the experiments with the chest cavity, a long incision was made in the fourth right interspace and through the parietal pleura. The sulfanilamide was then dusted on the visceral pleura and the incision closed with silk. In the case of the peritoneal cavity, a midline incision was made about midway between the symphysis pubis and the xyphoid of the sternum, the sulfanilamide being dusted over the intestines immediately under the omentum. For oral administration the drug was given in water suspension by way of a stomach tube. The sulfanilamide used was approximately a No. 100 mesh powder. All of the dogs were deprived of food for some twelve hours prior to the experimental procedures. A control blood sample was taken immediately before the administration of sulfanilamide and for the first six or seven hours at hour intervals, except in the case of three experiments concerned with absorption from the pleural surfaces, when the first samples were taken after thirty

minutes. In all cases a final sample was taken twenty-four hours after the sulfanilamide administration. The blood content of sulfanilamide was then determined by the method of Marshall and Litchfield.<sup>7</sup>

Table I gives the results of one series of studies in which the dose of sulfanilamide used in all three methods of medication was 100 mg. per kilogram of body weight. Four dogs were used for the pleural and gastrointestinal administrations, five for the peritoneal. The average blood concentrations are depicted graphically in Fig. 1. Statistical analyses indicated that there was no significant difference in the extent of sulfanilamide absorption from these various routes of administration. As is apparent from Table I, the greatest individual variation occurred in the dogs in which the drug was applied to the pleural cavity. In another experiment two dogs were given sulfanilamide (60 mg. per kilogram) by each of the three routes of administration with an interval of ten days between medications, and similar results were obtained. As judged from these animals, there seems to be just as much variation in the same dog in its response to sulfanilamide by the three modes of administration as there is between different dogs so treated.

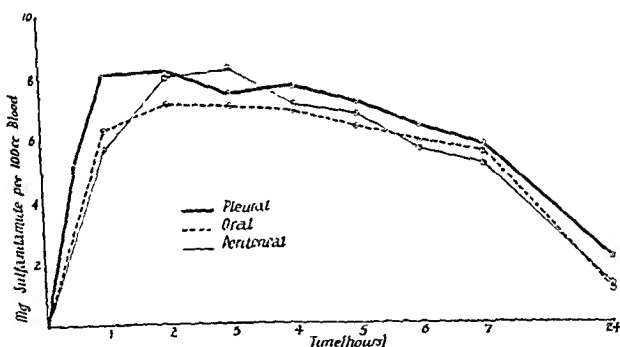


Fig. 1.—Comparative absorption rate of sulfanilamide in dogs following various routes of administration. Dose of sulfanilamide, 100 mg. per kilogram.

### CONCLUSIONS

In the normal dog sulfanilamide is equally well absorbed from the pleural cavity, peritoneal cavity, and gastrointestinal tract. Transference of these results to the use of sulfanilamide in a diseased chest or peritoneal cavity in man is, of course, difficult. These experiments, however, serve a useful purpose in calling attention to the possible magnitude of absorption from the pleural and peritoneal cavity, and hence to the need of some regard for the amount of sulfanilamide applied to these areas. They also suggest that such absorption be kept in mind, if in addition to its local use, other simultaneous sulfonamide therapy is contemplated.

TABLE I  
COMPARATIVE ABSORPTION RATE OF SULFANILAMIDE IN DOGS FOLLOWING VARIOUS ROUTES OF ADMINISTRATION

TIME (HR.)	MODE OF ADMINISTRATION (DOSE SULFANILAMIDE, 100 MG PER KG.)									
	PLEURAL CAVITY (4 DOGS)			PERITONEAL CAVITY (5 DOGS)			ORAL (4 DOGS)			STANDARD ERROR†
	AVERAGE MG. SULFANIL- AMIDE PER 100 C.C. BLOOD	STANDARD DEVIATION*	STANDARD ERROR†	AVERAGE MG. SULFANIL- AMIDE PER 100 C.C. BLOOD	STANDARD DEVIATION*	STANDARD ERROR†	AVERAGE MG. SULFANIL- AMIDE PER 100 C.C. BLOOD	STANDARD DEVIATION*		
1	5.2	2.56	1.48	5.7	1.41	0.63	6.3	1.26	0.63	
1	8.1	3.76	1.88	8.0	1.00	0.45	7.1	0.68	0.34	
2	5.2	2.71	1.36	8.2	1.34	0.60	7.0	0.45	0.22	
3	7.4	1.46	0.84	7.0	1.63	0.73	6.8	0.52	0.26	
4	7.6	1.03	0.52	6.7	1.39	0.62	6.3	0.14	0.07	
5	7.1	1.15	0.58	5.6	1.41	0.63	5.5	0.78	0.39	
6	6.3	0.39	0.20	5.1	1.35	0.60	5.0	1.58	0.79	
7	5.7	0.60	0.30	1.2	0.79	0.35	1.1	0.90	0.45	
24	2.1	0.75	0.38	0			0			
Control	0			0			0			

$\sqrt{\frac{2\sqrt{2}}{n}}$

$$\cdot \sqrt{\frac{2 \bar{V}_2}{N-1}}$$

$$t \sqrt{\frac{2 \bar{V}_2}{N-1}}$$

$$\sqrt{N}$$



It should finally be stressed that these results with sulfanilamide do not necessarily imply that with other sulfonamide drugs, such as sulfapyridine and sulfathiazole, similar absorption rates occur. These compounds need separate study.

We wish to express our appreciation to Dr. I. A. Bigger, Professor of Surgery, who suggested this problem and who has so freely given of his time in furthering it.

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	AVERAGE MG. SULFANIL- AMIDE PER 100 C.C. BLOOD	STANDARD DEVIATION*	STANDARD ERROR†	AVERAGE MG. SULFANIL- AMIDE PER 100 C.C. BLOOD	STANDARD DEVIATION*	STANDARD ERROR†	AVERAGE MG. SULFANIL- AMIDE PER 100 C.C. BLOOD	STANDARD DEVIATION*	STANDARD ERROR†	
1	3.2	2.56	1.48	5.7	1.41	0.63	6.3	1.26	0.63	
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3	7.4	1.46	0.84	7.0	1.63	0.73	6.8	0.52	0.26	
4	7.6	1.03	0.52	6.7	1.39	0.62	6.3	0.14	0.07	
5	7.1	1.15	0.58	5.6	1.41	0.63	5.5	0.78	0.29	
6	6.3	0.39	0.20	5.1	1.35	0.60	5.0	1.58	0.79	
7	5.7	0.60	0.30	1.2	0.79	0.35	1.1	0.90	0.45	
24	2.1	0.75	0.38	0						
Control	0			0			0			

$\cdot \sqrt{\frac{\sum \bar{V}^2}{N-1}}$

$$* \sqrt{\frac{\sum V^2}{N-1}}$$

$$† \sqrt{\frac{\sum V^2}{N-1}}$$

$$\sqrt{N}$$

Parker and her associates<sup>1, 20, 21</sup> were able to demonstrate that rabbits, which had been immunized by the intravenous injection of small doses of dermonecrotxin, developed an antiserum in their blood which would protect normal rabbits against staphylococcal toxin, and that the serum was capable of neutralizing the toxin both in vivo and in vitro. Burnet<sup>22</sup> in 1929, working independently, confirmed her work. Pantou and Valentine<sup>23</sup> came to the conclusion that the important antibody in the antisera is antileucocidin. Even though toxins of individual strains are capable of producing an antiserum which contains all of the antibodies, the proportion of these antibodies in the different antisera varies greatly one from the other. Some are capable of producing a serum with a high antihemolysin titer and a low antileucocidin titer, while another strain will develop a serum with a high antileucocidin and a low antihemolysin titer; thus different strains of staphylococci are capable of producing these antigens in varying strengths.

The data<sup>24-26</sup> obtained on natural and acquired immunity in human beings has for the most part been determined in studies of the antihemolysin titer of the blood and skin sensitivity to toxin. Even though the antihemolysin test measures only one antibody, it is the simplest and most reliable method of determining the amount of circulating antitoxin. In 1932 Bryce and Burnet<sup>24</sup> studied the antihemolysin levels in the sera of human beings in various age groups. They demonstrated that at birth there was a high titer which rapidly fell over a period of a few weeks to a very low titer. From this point there was a gradual increase in titer as the years advanced. Using the I. U. defined as "the specific neutralizing activity for staphylococcus toxin contained in 0.5 mg. of the standard preparation," the following workers found the antihemolytic titer in normal human sera to be: Murray,<sup>25</sup> 0.4 to 2 units; Blair and Hallman,<sup>29, 30</sup> 0.5 to 1 unit; Whitby,<sup>31</sup> 0.5 to 2 units; Dolman,<sup>32-34</sup> 0.3 to 1 unit; Nélis and Poncelet,<sup>35</sup> 0.15 to 1.5 units; and Buchman,<sup>36</sup> less than 1 unit. All these determinations were made in human beings who gave no history of staphylococcal infection.

Determinations of the antihemolysin titer of the sera from patients with staphylococcal infections have been made in order to study the acquired immunity which might be developed in these cases. The cases involving only the soft tissues show no measurable rise in antihemolysin titer of the sera. Whitby,<sup>31</sup> Dolman,<sup>32-34</sup> Murray,<sup>25</sup> and Parish and associates<sup>37, 38</sup> found the levels in their cases with infection to be the same as found in sera of normal patients free from staphylococcal infections. Connor and McKie,<sup>39</sup> on the other hand, report a definite elevation in the titer of cases with staphylococcus infection. This was particularly so in the patients with a carbuncle or a deep soft tissue abscess. In cases of osteomyelitis Dolman<sup>32-34</sup> and Murray<sup>25</sup> report a much higher titer ranging between 5 and 11.7 I. U. Nélis and Poncelet,<sup>35</sup> Blair and Hallman,<sup>29, 30</sup> Buchman,<sup>36</sup> and Whitby<sup>31</sup> found the titers in similar cases to

# STUDIES OF ANTIHEMOLYSIN LEVEL IN PATIENTS WITH STAPHYLOCOCCUS INFECTIONS TREATED WITH STAPHYLOCOCCUS TOXOID

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SINCE the discoveries of sulfanilamide and its related compounds, attention has been focused more toward the treatment of acute infections with these newer drugs than toward the prevention of the occurrence of these infections. These drugs have proved to be very effective in the treatment of infections caused by many varieties of bacteria. Recent reports indicate that sulfathiazole should prove more effective than either sulfanilamide or sulfapyridine in the treatment of staphylococcal infections. In spite of the accumulating evidence that sulfathiazole is to some degree effective in staphylococcal infections, further study is necessary before definite conclusions as to its value can be made. However, in this newer enthusiasm we must not lose sight of the fact that the prevention of these infections is of much greater importance.

Even though Parker<sup>1</sup> is credited with creating the recent stimulus to the study of staphylococcal toxins and antitoxins, most of the actions of staphylococcal toxins had been observed by workers prior to her report. Van de Velde<sup>2</sup> in 1890 observed that leucocidin destroyed white blood corpuscles. Necrosis of a rabbit's skin, following intradermal injections of staphylococcal filtrates, was reported in 1899 by von Lingelsheim,<sup>3</sup> and in 1900 Kraus and Clairmont<sup>4</sup> observed the hemolysis of mammalian erythrocytes in cultures of staphylococci. In the same year Kraus and Pribram<sup>5</sup> observed the killing of rabbits within 30 minutes following the intravenous injection of staphylococcal filtrates. Another property of staphylococcal metabolism, the capacity of coagulating plasma, was first described by Loeb<sup>6</sup> in 1903. It was not until Parker<sup>1</sup> reported her studies of the dermonecrotic and lethal toxins that the antigenic possibilities of these toxins were realized.

Since the report of Parker,<sup>1</sup> many workers<sup>7-11</sup> have been studying the antigenic properties of these toxins, both from a therapeutic point of view and as a means of stimulating antibodies to prevent the infections. Clinically, there is evidence that natural immunity to staphylococcal infections varies greatly with individuals. There are those who develop infections from the slightest exposure while others are able to resist or minimize these infections.

the 1 or 2 unit rise associated with lesions of the skin and subcutaneous tissues. Blair and Hallman<sup>29, 30</sup> found increases averaging between twelve- and twentyfold of the original titers. Buchman<sup>36</sup> and Hite and co-workers<sup>37, 38</sup> made a similar observation of rise in titer but felt that this increase of antihemolysin in the serum was no criterion of the clinical status of the case. Dolman<sup>33, 34</sup> likewise failed to observe much clinical improvement, even though he was able to raise markedly the titer of the blood. The results of these workers are not as encouraging in their cases of chronic osteomyelitis as were the findings in the cases of more superficial lesions.

The observations in this report were made on patients treated in the Presbyterian Hospital and Vanderbilt Clinic in New York City. All of them were suffering from either persistent or recurring staphylococcal lesions which had proved resistant to other forms of therapy. In all instances hemolytic staphylococcus was cultured from their lesions; in 5 of 9 cases of chronic osteomyelitis, nonhemolytic streptococcus also grew out.

The degree of immunity conferred was determined by observation of clinical improvement and the measurement of the antihemolysin titer of the sera. The antihemolysin titer was determined prior to the course of injections of toxoid, at intervals during the course of treatment, as well as at intervals for an indefinite time following the completion of the course of toxoid therapy. Even though the level of the antihemolysin titer does not necessarily accurately measure the degree of immunity developed, it is of value in that it has been used by other observers and forms a basis of comparison. As the follow-up on the cases has not been of sufficient duration to evaluate the incidence of recurrence following treatment, it will be impossible to do more than indicate the clinical value of pepsin-digested toxoid therapy in these patients.

This toxoid\* was prepared by the action of pepsin enzyme on staphylococcal filtrates of known toxin titers after the method of Parfentjev.<sup>39</sup> This toxoid was supplied to us in a concentrated form and appeared to have some distinct advantages over the formalin prepared toxoid. Observations made at the Lederle Laboratories show that the local and systemic reactions following the injections of the pepsin-digested toxoids did not appear as frequently and were not as severe as those reported when formalin toxoid was used. This was confirmed by us. It was also found that pepsin-digested toxoid could be given in concentrated form, thus obviating the multiple injections of the diluted toxoid followed by multiple injections of concentrated toxoid. It is also possible with this toxoid to increase rapidly the dosage to that which was used in all subsequent injections in these patients.

The types and number of these cases studied are given in the following table:

\*The toxoid used was a new preparation supplied by Lederle Laboratories.

be the same or only slightly elevated as compared with normal sera. These discrepancies in the findings only confuse the picture. On the other hand, they might be interpreted to mean that the antihemolysin titer of circulating blood tells only part of the story of existing immunity, and that in conjunction with the antihemolysin level, determination of the other antibodies should be performed.

Experimental work with staphylococcal toxin, antitoxin, and vaccines, though not encouraging, prepared the ground for the studies of staphylococcal toxoid as an immunizing agent. Employing Ramon's method, Burnet<sup>40, 41</sup> in 1931 showed that staphylococcal toxin could be detoxified with formalin and still retain antigenic properties. Since this time other methods<sup>42-46</sup> of detoxification have been tried and found to be nearly as effective. Studies by numerous investigators confirmed and added to the observations of Burnet. This work was again confirmed by Parish, O'Meara, and Clark.<sup>37</sup> They employed the antihemolysin test as their index of the degree of immunity conferred by the toxoid. Smith<sup>47, 48</sup> studied the spacing of the dose and quantity of each dose, and concluded that larger doses are more effective than smaller ones and that a better response was obtained when they were given at intervals of twenty-one to twenty-eight days. In 1936 Holm, Anderson, and Leonard<sup>45</sup> described their bacteriophage toxoid. Antihemolysin tests in rabbits treated with this showed higher titers than the control rabbits, which were treated with the regular toxoid or just bacteriophage.

The tremendous volume of experimental work which has appeared in the literature points to staphylococcal toxoid as the most effective method of elevating staphylococcal antihemolysin in rabbits. These rabbits are protected against injections of massive doses of toxin and living organisms. The transfer of this principle from the laboratory animal to the human patient has met with more or less success. The literature contains numerous reports of good results following the use of staphylococcal toxoid in patients suffering with acute and chronic staphylococcal infections. Many of the reports give the figures of the antihemolysin titer before, during, and after courses of toxoid therapy. Among the many workers with encouraging clinical results are Dolman,<sup>32-34, 49-51</sup> MacDonald,<sup>52</sup> Thygeson,<sup>53</sup> Ramon and co-workers,<sup>54</sup> Murray,<sup>28</sup> Whitby,<sup>31</sup> and Blair and Hallman.<sup>29, 30</sup> Each of these observers admits that he could not always correlate the clinical results with the antihemolysin response observed. Whereas in some cases those individuals showing the poorest antihemolysin response showed the best clinical results, others developed a high titer and a poor clinical result. Kindel and Costello,<sup>55</sup> as well as Cornbleet and Rattner,<sup>56</sup> failed to confirm the good results observed by the others. The work done in cases of chronic osteomyelitis has not been so encouraging from the clinical point of view. In contrast to the questionable clinical results is the more marked increase in antihemolysin titer in those cases as compared with

the 1 or 2 unit rise associated with lesions of the skin and subcutaneous tissues. Blair and Hallman<sup>29, 30</sup> found increases averaging between twelve- and twentyfold of the original titers. Buchman<sup>36</sup> and Hite and co-workers<sup>57, 58</sup> made a similar observation of rise in titer but felt that this increase of antihemolysin in the serum was no criterion of the clinical status of the case. Dolman<sup>33, 34</sup> likewise failed to observe much clinical improvement, even though he was able to raise markedly the titer of the blood. The results of these workers are not as encouraging in their cases of chronic osteomyelitis as were the findings in the cases of more superficial lesions.

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This toxoid\* was prepared by the action of pepsin enzyme on staphylococcal filtrates of known toxin titers after the method of Parfentjev.<sup>59</sup> This toxoid was supplied to us in a concentrated form and appeared to have some distinct advantages over the formalin prepared toxoid. Observations made at the Lederle Laboratories show that the local and systemic reactions following the injections of the pepsin-digested toxoids did not appear as frequently and were not as severe as those reported when formalin toxoid was used. This was confirmed by us. It was also found that pepsin-digested toxoid could be given in concentrated form, thus obviating the multiple injections of the diluted toxoid followed by multiple injections of concentrated toxoid. It is also possible with this toxoid to increase rapidly the dosage to that which was used in all subsequent injections in these patients.

The types and number of these cases studied are given in the following table:

\*The toxoid used was a new preparation supplied by Lederle Laboratories.

Osteomyelitis:	
a. Acute	1
b. Chronic	9
Soft tissue lesions:	
a. Furunculosis	16
b. Carbuncle	3
c. Axillary abscess	3
d. Pustular dermatitis	2
e. Recurrent infections of cutis over anterior closed space	1

These total 35 cases with 7 different manifestations of the infections caused by the staphylococcus organisms.

The toxoid was administered hypodermically into the subcutaneous tissues. Usually the size and frequency of the dose administered was determined by the patient's reaction to the injection. The reactions encountered or associated with the administration of toxoid can be classified as being local or systemic or both. In those patients showing a reaction, this usually would appear twelve to eighteen hours following the injection and persist eighteen to twenty-four hours after its appearance. The patients who developed a slight pain immediately after the injection and in whom this pain had subsided in four to eight hours are not included in the group of local reactions to be discussed. There are 19 patients who showed a definite local manifestation of longer than eighteen hours. In this group, 8 complained of only a slight pain which was not particularly annoying and in no way incapacitating. Examination of these patients was negative for swelling and redness, but in some there was a suggestion of slight thickening of subcutaneous tissues. There were 10 patients complaining of pain which was very bothersome, in many instances interfering with their daily routine. In such cases examination usually revealed local swelling with or without redness but with a more definite sense of thickening of the subcutaneous tissues. There were no patients with an associated lymphangitis or lymphadenitis. All of these reactions subsided with rest.

Systemic reactions were very infrequent, only 6 cases showing any general manifestation which could possibly be associated with the toxoid. In 5 of them, this reaction was purely subjective, the complaints being mainly those associated with loss of feeling of well-being. In 1 there was a definite pyrexia with associated chilly sensations. All cases with systemic manifestations had an associated local reaction of pain and swelling.

The routine, in amount of initial dose, rate of increase of dosage to the maximum single dose, and frequency of the dose, changed somewhat as our experience with this toxoid increased. In order to avoid marked local reactions and mild systemic reactions, the early cases received the toxoid as follows: initial dose, 0.1 c.c. of 1:10 dilution of toxoid; subsequent doses increased each time by 0.1 c.c. until a maximum of 0.9 c.c.



of 1:10 dilution had been reached. At this point the patient then received 0.1 c.c. of undiluted toxoid and a course of injections of increasing doses, with 0.1 c.c. added to each until the dose finally reached 1 c.c. undiluted toxoid. The injection would be given at intervals of three to seven days, varying somewhat with the presence or absence of a reaction. The total dose would equal approximately 6 c.c. of undiluted toxoid. In spite of the 1:10 dilution, local reactions were observed during the first part of this course. Because of the time consumed and the mildness of reactions, the routine in these cases was changed to the following program which was used in all of the later cases, comprising the majority of the series: Starting with 0.1 c.c. to 0.5 c.c. of undiluted toxoid, the dose would be increased to 1 c.c. as rapidly as the patient would tolerate it. In many cases this could be reached by the third injection, the second being 0.5 c.c. The remaining doses would be 1 c.c. of undiluted toxoid given at intervals of two to four days. A total dose of 6 to 8.5 c.c. was desired in each case. In a few instances therapy was stopped short of this total dose. However, this stopping of toxoid therapy before the desired dose of 6.5 c.c. had been reached was in no instance the result of either a systemic or local reaction to the toxoid. It usually was the result of the clearing of the infection and the consequent failure of the patient to return for further treatment. Contrary to our expectations, this rapid increase of dosage was not accompanied by any more reactions than by the older method of administration. Many of the patients did not have even local pain and could go through the series without interruption. In some instances reactions would appear about halfway through the course. When this occurred, the next dose was either postponed or cut in half. By this method it was possible to give the patients a complete course in fourteen to twenty-one days instead of prolonging it over a period of months, as the previous methods of administration required.

Most of the patients requiring and receiving only one such course of treatment showed some elevation of their antihemolysin titer before its completion. In cases which failed to show an increase, the toxoid was either continued until a total of 12 to 15 c.c. had been given or the patient was given a rest period of ten to fourteen days before starting a second series of six injections of 1 c.c. each. Attempts to maintain a high titer or to raise the titer above a maximum for an individual by continuing the toxoid were of little avail, since the peak titer would persist only a few days.

By making frequent determinations of the antihemolysin level, the relationship of the rate of rise to the amount of toxoid given and the time at which the maximum titer was first reached was observed.

Table I gives the titer found in the patients before they received toxoid.

TABLE I

LESION	NO. OF CASES AND INITIAL TITER											
	0.5-0.9	1	1.5	2	3	4	5	6	7-9	10-12	13-15	16-18
Chronic osteomyelitis	2			4	1			1				1
Acute osteomyelitis										1		
Furunculosis	5	3	4	3		1						
Carbuncle	3											
Axillary abscess	1	1		1								
Pustular dermatitis		2										
Recurrent anterior closed space infections		1										
Totals	11	7	4	8	1	1		1		1		1

The initial titers in these cases are similar to those found by other observers for the respective lesions. Whitby<sup>32</sup> reports titers in chronic osteomyelitis varying from less than 1 unit to a level above 5 units in the majority of his cases. Blair and Hallman<sup>29, 30</sup> report 64 of their cases with a titer of less than 3 units and only 16 with more than 3 units. Murray<sup>28</sup> reports 7 cases of chronic osteomyelitis with the average level of 11.7 units; Dolman<sup>33, 34</sup> found 5 to 10 units to be the normal range in his cases of chronic osteomyelitis; while Nêlis and Poncelet<sup>35</sup> found the titer in their cases to be less than 3 units. In cases of more superficial or soft tissue lesions, Whitby,<sup>31</sup> Blair and Hallman,<sup>29, 30</sup> and Murray<sup>28</sup> report all but 5 of a total of 415 cases to have less than 2 units, of which 337 had only 1 or less units of antihemolysin in the tested serum before receiving inoculation. In our series, including all types of lesions, 30 cases had 2 or less units in the tested serum. Of the remaining 5 cases, 4 belong in the group of osteomyelitis and had titers of 3, 6, 10, and 16 units. However, only 1 case in the soft tissue group had more than 2 units. From this it can be said that the majority of our osteomyelitis cases agree more closely with the findings of Nêlis and Poncelet<sup>35</sup> and Blair and Hallman.<sup>29, 30</sup>

As outlined previously, the frequency and amount of toxoid varied at times during the course of this investigation. Because of the irregularity with which we were able to obtain blood from the patients, it was difficult to correlate accurately the rate of rise in titer to the amount and frequency of the dose of toxoid. Figs. 1 and 2 and Tables II and III give the day at which maximum rise was obtained after starting the toxoid.

*Osteomyelitis.*—Fig. 1 represents the cases of osteomyelitis. Of these cases, 9 showed a definite elevation in their titer before the course of 6.5 c.c. of toxoid had been completed, of which 3 reached their maximum level. The maximum titer in the remaining 6 cases was obtained between three and forty days after discontinuing injections. The remaining case was very refractory, maintaining a level of 2 units even after receiving 12 c.c. of toxoid. However, this patient was given a total dose of 15.93 c.c. and thirty-five days after this was completed, or 140 days after

TABLE II  
OSTEOMYELITIS

CASE		1	2	3	4	5	6	7	8	9	10
Diagnosis*		Chr.	Chr.	Chr.	Chr.	Chr.	Chr.	Chr.	Chr.	Chr.	Ac.
Reaction	Local†	+	0	0	0	++	+	++	++	++	++
	Systemic‡	0	0	0	0	+	0	+	+	0	0
Dose ex.	Initial	0.1	0.25	0.01	0.05	0.3	0.3	0.5	0.01	0.01	0.2
	Average	1	1	1	1	1	1	0.75	1	0.9	1
	Total	3.4	15.95	5.6	6.0	5.3	5.3	5.5	15.95	6.7	3.5
Days between doses		3	5.7	1.5	3.7	2	2	3.5	4	4.7	5
Duration of toxoid: Days		17	105	12	35	10	10	33	118	84	17
Antihemolysin level	Before toxoid	2	2	<1	2	0.5	3	2	16	6	10
	Maximum	6	3	14	4	3.5	4	6	32	9	36
	Units change	4	1	13+	2	3	1	4	16	3	26
Units		6	3	1	3	3.3	2	3	28	6	32
Time to reach maximum: Days		27	140	10	77	18	14	46	17	30	33
Dose to reach maximum		5.4	15.95	1.5	6.0	5.3	5.3	5.5	4.5	1.5	3.5
Days at final reading		27	140	117	148	18	67	109	260	95	140

\*Diagnosis: Chr., chronic; Ac., acute.

†Local: +, pain; ++, pain and swelling.

‡Systemic: +, lethargy, headache, malaise.

TABLE I

LESION	NO. OF CASES AND INITIAL TITER											
	0.5-0.9	1	1.5	2	3	4	5	6	7-9	10-12	13-15	16-18
Chronic osteomyelitis	2			4	1			1				1
Acute osteomyelitis										1		
Furunculosis	5	3	4	3		1						
Carbuncle	3											
Axillary abscess	1	1		1								
Pustular dermatitis		2										
Recurrent anterior closed space infections		1										
Totals	11	7	4	8	1	1		1		1		1

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TABLE III  
SOFT TISSUE LESIONS

CASE		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Diagnosis*	P.D.	P.D.	P.D.	G	G	C	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	A.A.	A.A.	A.A.	A.C.
		+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reaction		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dose c.c.	Systemic	0.5	0.3	0.2	0.5	0.2	1	0.02	0.2	0.2	0.01	0.3	0.2	0.01	0.3	0.3	0.5	0.2	0.2	0.5	0.05	0.5	0.2	0.3	0.3	0.5
	Initial	1	0.5	1	1	1	1	0.09	1	1	1	0.5	1	0.3	1	1	1	1	1	1	1	1	1	1	1	1
	Average	6.0	5.6	5.5	5.0	6.2	3	5.7	10.5	7.2	6.0	4.7	20.5	4.8	6.3	6.5	6.5	8.5	6	6.3	23.9	15.8	8.2	6.8	5.3	6
Days between doses	Total	3	4-6	2	3	0	4	4-6	2-4	2	2-6	2-4	3	4	2-5	2-5	2	6-8	4	3	2-5	3	3	3-7	7	4
	Duration of toxoid: Days	19	50	14	24	12	8	68	32	14	40	26	66	39	31	30	17	86	31	24	150	120	20	23	35	20
Anti-hemolysin level	Before toxoid	1	1	<1	<1	<1	1	<1	4	1	<1	<1	1	14	1.5	2	1.5	2	<1	<1	<1	1.5	<1	1	2	1
	Maximum	3	3	5	2	6	2	3	6	3.5	2	14	8	2	3	3	4	1.5	2	3.5	4	4	3	5	1.5	2
Units	Units change	2	2	4	1	5	1	2	2	2.5	1	13	7	21	1.5	1	3	-0.5	0	2.5	3	2.5	2	4	-0.5	1
	Final Level	3	1	2	1	2	1	2.5	2	1.5	1	6	8	2	3	1.5	4	1.5	2	3.5	1	3	1.5	4	1.5	0.5
Time to reach maximum: Days		22	40	28	17	22	7	76	32	14	12	17	114	25	31	22	10	29	-	15	220	60	27	16	-	13
	Dose to reach maximum c.c.	6	2.5	5.5	3	6.2	2	5.7	9.5	6.2	0.9	2	20.5	2.6	5.3	3.5	3.5	-	-	6.3	23.9	8.5	8.2	2.9	-	3.2
Days to final reading		39	135	97	74	95	150	144	110	84	90	124	114	39	31	88	17	58	57	85	284	165	70	65	-	80

\*P.D., Puscular dermatitis; O, carbuncle; F, furunculosis; A.A., axillary abscess; A.C., anterior closed space (recurrent).

+, Pain (local), lethargy, malaise (general); ++, pain and swelling (local), malaise and pyrexia (general).

starting the treatment, the titer went up to 3 units. In the majority of the cases, the maximum antihemolysin titer was reached within forty days after starting therapy. The average elevation of the maximum titer over the initial titer was only 2 to 4 units, only 3 cases showing a more marked elevation of 13, 16, and 24 units respectively. The highest titer

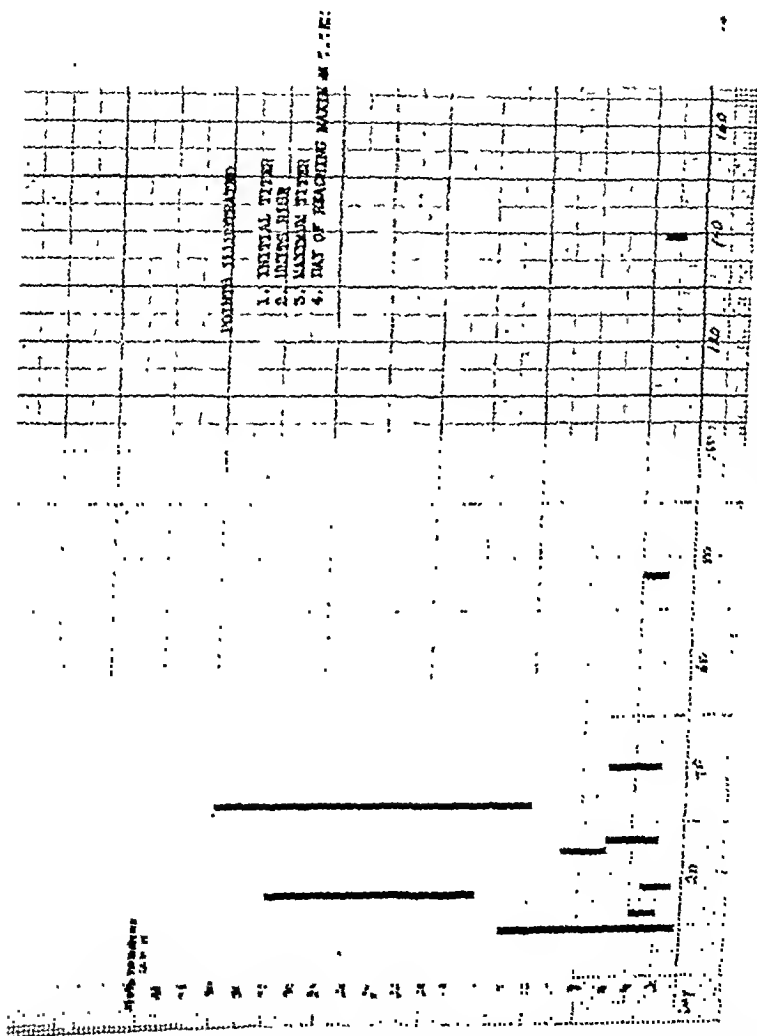


Fig. 1.—Osteomyelitis cases.

in 6 cases was less than 6 units. The highest titer obtained in any one patient was in the case of acute osteomyelitis who reached a level of 24 units above his initial titer.

It is difficult to correlate clinical results in cases of chronic osteomyelitis in so short a period of observation. It is fair to say that in 8 cases observed, sinuses continued to drain, and there was little evidence of local improvement.

TABLE III

## SOFT TISSUE LESIONS

CASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Diagnosis*	P.D.	P.D.	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	A.A.	A.A.	A.A.	A.C.
Reaction	+	+	0	++	0	±	0	0	++	0	++	0	++	±	++	0	0	0	++	0	0	0	+	++	+
Dose c.c.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Initial	0.5	0.3	0.2	0.5	0.2	1	0.02	0.2	0.2	0.01	0.3	0.2	0.01	0.3	0.5	0.5	0.2	0.2	0.5	0.05	0.5	0.2	0.3	0.3	0.5
Average	1	0.5	1	1	1	1	0.09	1	1	1	0.5	1	0.3	1	1	1	1	1	1	1	1	1	1	1	1
Total	6.0	5.6	5.5	5.0	6.2	3	5.7	10.5	7.2	6.0	4.7	20.5	4.8	6.3	6.5	6.5	8.5	6	6.3	23.9	15.8	8.2	6.8	5.3	6
Days between doses	3	4-6	2	3	0	4	4-6	2-4	2	2-6	2-4	3	4	2-5	2-5	2	6-8	4	3	2-5	3	3	3-7	7	4
Duration of toxoid: Days	19	50	14	24	12	8	68	32	14	40	26	66	39	31	36	17	86	31	24	150	120	20	23	35	20
Before toxoid	1	1	<1	<1	<1	1	<1	4	1	<1	<1	1	1+	1.5	2	1.5	2	2	<1	<1	1.5	<1	1	2	1
Antihemolysin level	3	3	5	2	6	2	3	6	3.5	2	14	8	2	3	3	4	1.5	2	3.5	4	4	3	5	1.5	2
Units change	2	2	4+	1+	5+	1	2+	2	2.5	1+	13+	7	±1	1.5	1	3	-0.5	0	2.5+	3+	2.5+	2+	4	-0.5	1
Final Level	3	1	2	1	2	1	2.5	2	1.5	1	6	8	2	3	3	4	1.5	2	3.5	1	3	1.5	4	1.5	0.5
Time to reach maximum: Days	22	40	28	17	22	7	76	32	14	12	17	114	25	31	22	10	29	-	15	220	60	27	16	-	13
Dose to reach maximum c.c.	6	2.5	5.5	3	6.2	2	5.7	9.5	6.2	0.9	2	20.5	2.6	5.3	3.5	3.5	-	-	6.3	23.9	8.5	8.2	2.9	-	3.2
Days to final reading	39	135	97	74	95	150	144	110	84	90	124	114	39	31	88	17	58	57	85	284	165	70	65	-	80

\*P.D., Pustular dermatitis; C, carbuncle; F, furunculosis; A.A., axillary abscess; A.C., anterior closed space (recurrent).

±, Pain (local), lethargy, malaise (general); ++, pain and swelling (local), malaise and pyrexia (general).

A case of chronic osteomyelitis following a compound fracture of the humerus three years previous to admission and during which time there was a persistent sinus illustrates that in certain cases it may be necessary to employ other forms of therapy to control mixed and complicated infections. Culture of this lesion grew out both hemolytic *Staphylococcus aureus* and a hemolytic streptococcus. At operation the sinus tract was excised and a sequestrum removed. Postoperatively the patient was given sulfanilamide by mouth; potent bacteriophage was applied locally as an irrigation and a wet dressing, and staphylococcal pepsin-digested toxoid was given hypodermically. The lesion healed rapidly, being completely healed in about three weeks. Likewise, in 1 of the cases of acute osteomyelitis which did exceptionally well, multiple forms of therapy were used in conjunction with the toxoid; the part played by toxoid therapy in this improvement cannot be evaluated in that surgery and sulfapyridine were used concomitantly. Another patient with chronic osteomyelitis failed to show improvement but felt a marked beneficial effect in a subjective sense. If the antihemolysin level was maintained above 28 International Units, he would lose his lethargy and despondency, his appetite would improve, and he would begin to put on weight. During the intervals when he was not receiving toxoid, his antihemolysin level would drop below 28 International Units, and with each fall of the level, there would be complete reversion to his old status.

*Soft Tissue Lesions.*—In the soft tissue group of this series, the response was generally of much less magnitude than was observed in the case of osteomyelitis. A total elevation of titer of less than 3 units was shown in 16 cases, 6 showing elevations from 3.5 to 13.5 units. In 2 cases a depression of the titer was observed, and in 1 there was no change. Of the 22 cases showing some elevation, this appeared early in the course of treatment in 21 of them. There were 18 cases showing a definite elevation before the course had been completed, 13 of these cases reaching a maximum level before or at the reading taken at the last toxoid dose. In 6 cases the maximum titer was reached from five to thirty-five days after the course had been completed. From Fig. 2 it can be readily seen that all but 6 of the cases had reached their maximum level by the twenty-eighth day or four weeks after starting inoculation. There are 2 cases which showed a persistent low titer but which rose 2 to 4 units before completion of a second series of doses. Table IV gives a general idea of the clinical results in these cases. In this table the heading "recurrence" lists those patients which became free of their staphylococcal infection but would return with a new lesion elsewhere; "no change" refers to those in whom the local lesion neither improved nor became worse during or following a course of toxoid therapy; "improved" lists those who showed a definite regression of their lesions with a distinct clinical relief, while the last column refers to



those whose lesions cleared during the course of therapy and in whom there was no recurrence when seen at the last follow-up visit to the clinic. It will be necessary to see these patients at regular intervals over a longer period before a final result can be discussed.

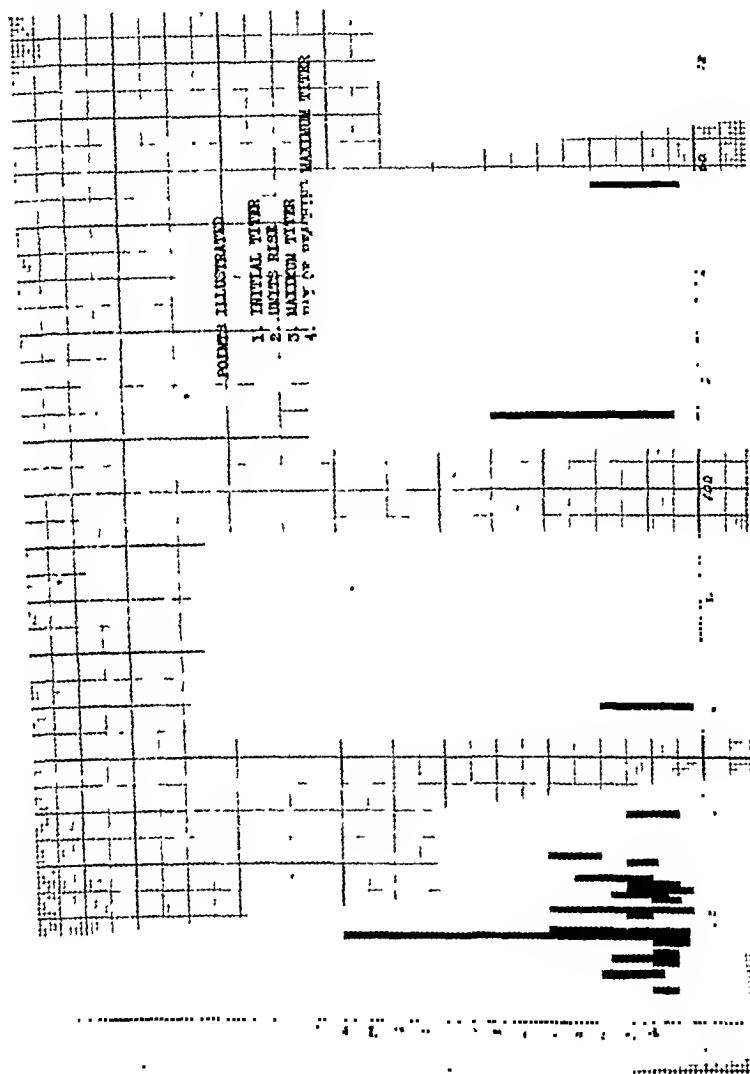


Fig. 2—Soft tissue lesions.

In the series of 11 cases of titer, there were 7 cases which failed to show beneficial clinical response, 4 of which had definite recurrence of the lesions. The 7 cases classified as improved might well fall into a group of probably cured cases if in the follow-up period they do not develop a recurrence. The 11 cases listed as probably cured are those begun early in the series and which remained cured to date. Consequently, as all but 1 or 2 of these cases had had persistent and recurring

TABLE IV

UNITS CHANGE IN TITER	RECURRENCE	NO CHANGE	IMPROVED	PROBABLE CURE
~ (Fall)		1	1	
0	1		1	1
1		1	1	5
2		1	2	2
3	1		1	2
4	1			
5			1	
6	1			
14				1
Total	4	3	7	11

infections which failed to respond to numerous measures, the results are considered as favorable.

In attempting to correlate the clinical results with elevation of the titer, it is interesting to note that 1 case showing a fall of 1 unit after treatment was definitely improved, if not completely relieved. There were 3 cases showing an increase of 3 or more units which were considered failures. Of the 18 cases listed as improved or cured, 16 had increase of less than 3 units. It is therefore impossible and, from our findings, definitely misleading to conclude that clinical improvement and elevation of antihemolysin titer parallel each other.

Attempts to maintain a high titer met with little or no success. No attempts were made to study this point in this series. One patient with osteomyelitis who showed subjective improvement without local change as long as his titer was maintained at a high level has been mentioned. This patient reached a maximum titer of 32 units on the twenty-seventh day. The first series of toxoid was started and the level returned to 28 units, which we have been able to maintain by giving 1 c.c. of toxoid every two days. In general it might be said that once the maximum level has been reached and the dose of toxoid discontinued, there is a gradual lowering of the titer. In all but one of the cases where this observation has been made, the final level reached is only slightly higher than the initial titer. This level would be reached usually in a period of six to twelve weeks. The exception in this case is a patient with acute osteomyelitis who 140 days from the start of therapy and 123 days since the last dose of toxoid had a level of 32 units, only 4 units below the maximum level which was reached on the twenty-fourth day after treatment had been begun.

At present, surgery and physiologic support are our greatest weapons against staphylococcal infections. We are all familiar with their limitations and with the results. Consequently, nothing more need be mentioned than that these weapons serve only in helping control the immediate infection.

The value of toxoid therapy is at present going through a trial phase both experimentally and clinically. Experiments with rabbits show

that it has definite immunologic benefits for these animals. The work with patients, on the other hand, is not as convincing. In the past few years articles showing good results with many cases but a large number of failures with others have appeared in the literature. Most of them support its use and make great claims of its effectiveness. Its value in acute toxic conditions has not been thoroughly investigated. In view of the reports of failures as measured by the antihemolysin titer, it is obvious that this index does not necessarily indicate the degree of immunity present. The question of specificity of a toxoid to a given strain, as well as many other phases of this work, should be investigated. Much of this is being studied and when complete should give a more reasonable answer to the question of the value of toxoid in treating and preventing staphylococcal infections.

#### SUMMARY

1. The value of treating chronic staphylococcal infections with the injection of staphylococcal toxoid has been discussed. Experimental and clinical evidence indicates that this form of therapy might be of benefit in certain cases of this disease.

2. In this series of patients treated, multiple and fairly large doses of concentrated pepsin-digested toxoid were injected subcutaneously. No severe or alarming reactions were observed in any of these patients, and in only a few instances was the local reaction severe enough to delay the usual routine of progressive dosage.

3. In all cases the change in the antihemolysin titer of the blood was compared with the antihemolysin level existing before therapy was started. In 32 cases, a definite elevation of titer was observed, and only 3 cases showed no elevation of titer.

4. In no instance was the patient made worse by this form of therapy.

#### CONCLUSIONS

1. Pepsin-digested toxoid was effective in raising the antihemolysin titer in 32 patients with recurrent staphylococcal infections. There were 3 cases which failed to show any elevation of antihemolysin following pepsin-digested toxoid.

2. Pepsin-digested toxoid can be safely administered in cases of recurrent furunculosis. However, in view of the fact that pepsin-digested toxoid contains foreign protein, the possibility of reactions in a number of cases must be kept in mind.

3. As the patients in this series have not been followed for a sufficiently long time to allow for correct evaluation of this method of treatment, no definite conclusions can be drawn as to its clinical efficacy. However, as many of the cases showed immediate clinical improvement, toxoid therapy can be considered an adjunct to other forms of therapy.

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# THE INACTIVATION OF GROUP-SPECIFIC ISOAGGLUTININS IN RELATION TO THE TRANSFUSION OF INCOMPATIBLE PLASMA, SERUM, AND ASCITIC FLUID

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THE last few decades have witnessed the increasing utilization of blood transfusion in biological and clinical fields. It is only recently, however, that blood plasma and blood serum have come into general use, despite the fact that they had been used by Guthrie and Pike<sup>1</sup> in 1907 for the treatment of experimental hemorrhage. These workers reported favorably on its use and their findings were confirmed by Mann,<sup>2</sup> Rossius,<sup>3</sup> and Kallius.<sup>4</sup> Little distinction was made by these early workers between blood plasma and blood serum. However, Richet, Brodin, and Saint-Girons<sup>5</sup> obtained better results in experimental hemorrhage with plasma transfusions than with serum transfusions. The reason for the difference in the effects of plasma and of serum is not clear, although a clue is provided by the work of Stevens and Lee,<sup>6</sup> who noted that vasotonins were more apt to appear in blood serum than in blood plasma. When it is realized that, while some of these vasotonins are vasopressor, there does occur a formation of vasodepressor substances, the differentiation of serum from plasma takes on a new significance. Stewart and Harvey<sup>7</sup> investigated one of these vasodepressor substances and came to the conclusion that it was a protein of the albumin type. Many of these vasotonins, both pressor and depressor, disappear from plasma and serum within twenty-four hours after withdrawal from the body (Freund<sup>8</sup>). Nevertheless, they may persist indefinitely (Bayliss and Ogden<sup>9</sup>).

Despite the establishment of an experimental basis for the use of plasma and serum in clinical practice, it was not until a decade after the work of Guthrie and Pike<sup>1</sup> that the transfusion of plasma and serum into human beings was carried out. The isolated reports of Payne and Steen<sup>10</sup> and of Mairano and Teneff<sup>11</sup> were followed by the work of Kunz,<sup>12</sup> in 1932, who administered blood serum for hemorrhage in human beings. His favorable results were confirmed by Filatov and Kartaševskij,<sup>13</sup> in 1935. These workers transfused plasma obtained from Group AB blood into patients suffering from hemorrhage, burns, and traumatic shock. They found that plasma could be conserved in a refrigerator for periods of 10 to 330 days without affecting adversely the results of its transfusion. Their work was confirmed by others (Bureeva,<sup>14</sup> Alovski and Bureeva,<sup>15</sup> and Heinatz and Sokolow<sup>16</sup>). It is interesting to note that the percentage of reactions ranged up to 67.6.

Along similar lines was the work on the utilization of ascitic fluid as a transfusion agent. The encouraging results obtained with this fluid in experimental hemorrhage (Davis and White<sup>17</sup>) led to its use in human beings suffering from acute loss of blood (Davis and Blalock<sup>18</sup>) and from hypoproteinemia (Maes and Davis<sup>19</sup>).

In all of these studies with plasma, serum, or ascitic fluid, care was taken to determine the compatibility of the transfusion fluid with the blood of the prospective recipient. Recently, it has been suggested that the preliminary typing of plasma and serum is unnecessary (Tatum, Elliot, and Nessett<sup>20</sup>) and, accordingly, plasma has been transfused without preliminary cross-matching into human beings (Strumia and co-workers<sup>21</sup>).

The problem now arises as to what happens to the incompatible isoagglutinins when they are transfused into the blood of the recipient in the form of plasma, serum, or ascitic fluid. A clue to the solution is provided by the work of Landsteiner and Levine,<sup>22</sup> who in 1926 demonstrated the presence of substances in spermatozoa which are capable of suppressing the isoagglutinin activity of Group A or B sera. Since that time it has been shown that such substances are present in almost all of the tissues of man. Schiff<sup>23</sup> pointed out, in quantitative experiments, that the pancreas is richest in these group-specific substances.

The present investigation was undertaken to determine what factors are involved in the inactivation of group-specific substances.

*Method.*—The investigation was carried out in three parts.

1. An *in vitro* study of the inactivation of isoagglutinins was made. The tube and slide method was used. Group O ascitic fluid was mixed with varying amounts of Group A or B plasma. In other experiments varying amounts of Groups A and B plasma were mixed. The presence or absence of inactivation of isoagglutinins was determined by using Group A or Group B red blood cells suspended in 0.85 per cent sodium chloride solution. In one series of studies, citrated whole blood (Group A) was used as the testing material. The presence or absence of agglutination was determined in all instances by microscopic examination. Mixtures of plasma and isotonic sodium chloride solution served as controls. Under these circumstances the effects of temperature, dilution, and time upon the inactivation of isoagglutinins were studied.

2. The effect of transfusion of incompatible ascitic fluid into dogs was studied. The dogs, weighing from 10 to 20 pounds, were anesthetized with pentobarbital sodium in appropriate amounts. The arterial blood pressure obtained from the right carotid artery was recorded in the usual manner. Examinations for the presence of agglutination of the red blood cells in the recipient animals were carried out upon blood obtained from an ear of each animal.

3. Incompatible ascitic fluid was transfused into six patients. The method of collection, examination, and storage of the fluid has been

described in previous publications. The ascitic fluid was administered by vein, each 1,000 c.c. of fluid containing 50 c.c. of 5 per cent sodium citrate solution.

*In Vitro Experiments.*—It soon became obvious from our *in vitro* studies that the isoagglutinins present in plasma, serum, or ascitic fluid could be inactivated by appropriate mixture with a fluid containing opposing isoagglutinins. This is apparent from Table I, in which is illus-

TABLE I  
INFLUENCE OF TEMPERATURE FACTOR IN INACTIVATION OF ISOAGGLUTININS

PLASMA MIXTURE*	GROUP A ERYTHROCYTES SUSPENDED IN 0.85 PER CENT NaCl SOLU- TION†	GROUP B ERYTHROCYTES SUSPENDED IN 0.85 PER CENT NaCl SOLUTION
1. Control at 37° C. for 60 min.		
Ascitic fluid (O) (1)	+	+
Ascitic fluid (O) (2)	+	+
Group A plasma (1 c.c.) plus 0.85 per cent NaCl solution (1 c.c.)	-	+
Group B plasma (1 c.c.) plus 0.85 per cent NaCl solution (1 c.c.)	+	-
2. Incubation at 37° C. for 60 min.		
Group A plasma (1 c.c.) plus B plasma (1 c.c.)	-	-
Group A plasma (1 c.c.) plus Group O ascitic fluid (1 c.c.)	-	+
Group B plasma (1 c.c.) plus Group O ascitic fluid (1 c.c.)	+	-
3. Incubation at 26° C. for 60 min.		
Group A plasma (1 c.c.) plus B plasma (1 c.c.)	+	+
Group A plasma (1 c.c.) plus Group O ascitic fluid (1 c.c.)	+	+
Group B plasma (1 c.c.) plus Group O ascitic fluid (1 c.c.)	+	+
4. Incubation at 5° C. for 72 hr.		
Group A plasma (1 c.c.) plus B plasma (1 c.c.)	+	+

\*The plasma-ascitic fluid mixtures were incubated for 60 minutes at the various temperatures indicated before being added to the suspensions of red blood cells for reincubation.

†+, Agglutination after incubation at 37° C. for 45 minutes of red cell suspensions and plasma or ascitic fluid mixtures; -, no agglutination under similar circumstances.

trated the fact that a mixture of Group A and Group B plasma in equal proportions will inactivate the isoagglutinins in both plasmas so that neither will agglutinate suspensions of Group A or Group B red blood cells. This is the simplest illustration of the mutual suppression of isoagglutinins. The situation is more complex when one is dealing with a fluid of Group O type which contains both a and b isoagglutinins. However, it is possible to remove the activity of both a and b isoagglutinins, as the following protocol will illustrate:



## Protocol 2.—

1. 0.5 c.c. plasma (Group A) and 0.5 c.c. ascitic fluid (Group O) were incubated at 37° C. for 1 hour.
2. 0.5 c.c. plasma (Group B) and 0.5 c.c. ascitic fluid (Group O) were incubated at 37° C. for 1 hour.
3. Mixtures 1 and 2 were mixed and incubated at 37° C. for 1 hour.
4. The resultant mixture agglutinated neither Group A nor B red blood suspensions.

In other words, a fluid which agglutinates both Group A and Group B cells (Group O ascitic fluid) was converted into one which agglutinated neither Group A nor B cells; that is, into a universal donor fluid.

*Influence of Temperature Upon Isoagglutinin Inactivation.*—The optimal temperature for the inactivation of isoagglutinins in various plasma and/or ascitic fluid mixtures is 37° C. Lowering the temperature results in a prolongation of the process of inactivation (Table I). At temperatures of 26° C. or below, isoagglutinin inactivation may not occur or may be so delayed that agglutination occurs. This suggests that the mechanism of inactivation is dependent upon some chemical rather than physical change in the mixtures. The process of inactivation of isoagglutinins under optimal conditions can be completed within ten minutes; whereas, that of agglutination is usually not completed in less than thirty to sixty minutes. It is significant that the maximal degree of isoagglutinin inactivation occurs at temperatures which approximate that of the human body.

*Influence of Volume Upon Isoagglutinin Inactivation.*—In mixtures of plasma and/or ascitic fluid containing different isoagglutinins, the degree of inactivation of such isoagglutinins will depend not only upon temperature but also upon the relative amounts of fluid used. The isoagglutinin titers of plasma and of ascitic fluid obtained from different sources show marked variations. Thus, in these studies it has been found that, when suppression of the isoagglutinins of any given amount of plasma or ascitic fluid is desired, the results will be most certain if an equal amount of fluid containing the opposing isoagglutinins is added. However, this ratio of 1:1 may be altered to 1:1.5 or even to 1:2.3 (Table II). It is apparent that the relative amounts of fluid which are to be used will be dependent upon the isoagglutinin titer of each fluid. When these titers are unknown, it will be found that the safe volume ratio is 1:1.

Now the question raises itself as to the influence of the blood cells in the inactivation or suppression of the isoagglutinins of plasma or ascitic fluid which is added to blood of an opposite group. In Table II is illustrated the relative capacity of plasma and of whole blood to inactivate the isoagglutinins of Group O ascitic fluid. A volume ratio of 1:4 of plasma and ascitic fluid will not produce inactivation of the isoagglutinins in the ascitic fluid against either Group A or Group B cells. However, a similar volume ratio between plasma (Group A) which con-

TABLE II  
INFLUENCE OF VOLUME FACTOR UPON INACTIVATION OF ISOAGGLUTININS

GROUP O	GROUP A PLASMA (C.C.)	VOLUME RATIO PLASMA- ASCITIC FLUID	GROUP A RED CELL SUSPEN- SION*	GROUP O ASCITIC FLUID (C.C.)	GROUP B PLASMA (C.C.)	VOLUME RATIO PLASMA- ASCITIC FLUID	GROUP B RED CELL SUSPEN- SION	GROUP O ASCITIC FLUID (C.C.)	GROUP A WHOLE BLOOD (C.C.)	PLASMA CONTENT OF BLOOD (C.C.)	VOLUME RATIO PLASMA- ASCITIC FLUID	AGGLUTINA- TION
0.995	0.005	1:199	+	0.995	0.005	1:199	+	2	4	2	1:1	-
0.990	0.01	1:99	+	0.990	0.01	1:99	+	2	2	1	1:2	-
0.975	0.025	1:39	+	0.975	0.025	1:39	+	2	2	1	1:3	-
0.95	0.05	1:19	+	0.95	0.05	1:19	+	4	2	1	1:4	-
0.9	0.1	1:9	+	0.9	0.1	1:9	+	6	2	1	1:6	+
0.8	0.2	1:4	+	0.8	0.2	1:4	+					
0.7	0.3	1:2.3	-	0.7	0.3	1:2.3	+					
0.6	0.4	1:1.5	-	0.6	0.4	1:1.5	+					
0.5	0.5	1:1	-	0.5	0.5	1:1	-					

\*+, Agglutination; -, absence of agglutination.

tains an equal volume of red blood cells (Group A) and ascitic fluid (Group O) results in a suppression of the isoagglutinins of the ascitic fluid so that no agglutination takes place (Table II). It is evident, therefore, that the red blood cells take an active part in suppressing antagonistic isoagglutinins which are added to them. It would be of interest to determine the relative ability of the red blood cells and of the plasma of whole blood to inactivate antagonistic isoagglutinins. No conclusive data have been obtained regarding this aspect of the problem, although preliminary studies would seem to indicate that plasma and serum are the more effective portions of whole blood in this respect.

*Rate of Isoagglutinin Inactivation.*—The process of agglutination, in general, takes place in two stages: (1) the union of the antigen with the antibody, and (2) the agglutination or clumping of the cells. In vitro the agglutination reaction takes 30 to 120 minutes to be completed. In view of this fact, it was of interest to determine the length of time required for the completion of the process of isoagglutinin inactivation. Under optimal conditions of temperature ( $37^{\circ}\text{C.}$ ) and of volume (1:1 ratio), the inactivation of isoagglutinins in ascitic fluid (Group O) by plasma (Group B), using Group B cell suspensions as the testing material, is complete in 10 minutes but not in 5 minutes. The end point apparently lies between these two intervals of time (Table III). It is evident, therefore, that the process of isoagglutinin suppression is more rapidly completed than that of agglutination.

TABLE III  
INFLUENCE OF TIME FACTOR UPON INACTIVATION OF ISOAGGLUTININS

MIXTURE	PERIOD OF INCUBATION AT $37^{\circ}\text{C.}$ (MIN.)	EFFECT ON GROUP B CELLS*
Plasma B (0.2 c.c.) plus ascitic fluid O (0.2 c.c.)	0	+
	5	+
	10	-
	15	-
	20	-
	25	-
	30	-
	35	-
	40	-
	45	-
	50	-
	55	-
	60	-

\*+, Agglutination; -, absence of agglutination.

*Transfusions of Incompatible Ascitic Fluid in Animals.*—While in vitro studies revealed the importance of such factors as temperature and volume in the phenomenon of isoagglutinin inactivation, it was necessary to determine their significance in vivo. Group O ascitic fluid was used throughout. After being heated slowly to body temperature, the fluid was allowed to flow into the right femoral vein of each animal at a rate of 10 c.c. per minute. Previous cross agglutination tests were performed

and only those animals whose bloods were incompatible with the ascitic fluid *in vitro* were selected. The animals (dogs) were subjected to graded hemorrhage before transfusion. The results of this group of experiments are presented in Table IV and from these results two conclusions can be drawn: (1) the transfusion of a heterologous fluid containing incompatible isoagglutinins is tolerated by dogs, and (2) sufficient amounts of such a fluid to produce recovery from severe hemorrhage may be administered without producing evidences of agglutination of the red blood cells in circulation. Examination of the urines of these animals revealed an absence of hematuria and hemoglobinuria. It should be emphasized that the amounts of ascitic fluid administered to these animals were relatively large and would be equivalent to transfusions of 3,000 to 5,000 c.c. of ascitic fluid in man. Since the usual quantity of fluid transfused in man is only 500 to 1,000 c.c., it is obvious that the margin of safety is wide. No attempt was made to estimate the largest amount of fluid which could be tolerated.

*Transfusions of Incompatible Ascitic Fluid in Man.*—In order to complete this investigation, it was necessary to study the effect of the transfusion of incompatible ascitic fluid into human beings. The blood of the prospective human recipient was cross-matched with the ascitic fluid which was to be used for transfusion. The presence of definite agglutination of the red blood cells after incubation for forty-five minutes at 37° C. with the fluid was considered to be evidence of incompatibility. Using this criterion, six patients who were suffering from various minor forms of chronic infection were selected. The ascitic fluid after filtration was slowly heated to body temperature and administered by the intravenous route to each patient at a rate of 5 c.c. per minute. The amounts transfused varied from 200 to 415 c.c. A brief rigor occurred in two patients, while the other four patients showed no reaction (Table V). Upon blood examination, no evidences of agglutination were found in any of the subjects. Urinalysis revealed no albuminuria, hematuria, or hemoglobinuria. The ratio of the volume of ascitic fluid administered to the blood volume calculated from the body weight varied in four of the patients from 1:10.4 to 1:18.2 (Table V). In other words, the amount of fluid administered varied from 5 to 10 per cent of the calculated total blood volume. This is well within the limits of safety, inasmuch as *in vitro* studies have indicated that whole blood is capable of inactivating twice its own volume of ascitic fluid (Table II). The absence of agglutination in the blood of these patients after receiving incompatible ascitic fluid in quantities up to 415 c.c. suggests that the phenomenon of isoagglutinin inactivation occurs *in vivo* as well as *in vitro*.

#### COMMENT

It would seem pertinent at this point to discuss further the influence of temperature upon the inhibition of isoagglutinins. From the data al-

TABLE IV  
INFLUENCE OF TRANSFUSIONS OF INCOMPATIBLE ASCITIC FLUID IN EXPERIMENTAL HEMORRHAGIC SHOCK

EXPERIMENT NO.	DOG WEIGHT (KG.)	BLOOD REMOVED (C.C.)	BLOOD PRESSURE MM. HG (SYSTOLIC)			CALCULATED BLOOD VOLUME (C.C.)	CALCULATED BLOOD VOLUME AFTER HEMORRHAGE (C.C.)	AMOUNT OF ASCITIC FLUID	VOLUME: BLOOD: ASCITIC FLUID	RESULT
			BEFORE HEMORRHAGE	AFTER HEMORRHAGE	AFTER TRANSFUSION					
7	4.8	210	175	70	110	432	222	322	1:1	Recovery
8	7.7	295	155	25	125	693	398	477	1:1.2	Recovery
11	6.0	205	145	35	120	540	335	500	1:1.5	Recovery
4	6.4	370	165	20	115	576	206	450	1:2.2	Recovery
2	3.2	130	160	35	95	288	158	300	1:1.9	Recovery

and only those animals whose bloods were incompatible with the ascitic fluid in vitro were selected. The animals (dogs) were subjected to graded hemorrhage before transfusion. The results of this group of experiments are presented in Table IV and from these results two conclusions can be drawn: (1) the transfusion of a heterologous fluid containing incompatible isoagglutinins is tolerated by dogs, and (2) sufficient amounts of such a fluid to produce recovery from severe hemorrhage may be administered without producing evidences of agglutination of the red blood cells in circulation. Examination of the urines of these animals revealed an absence of hematuria and hemoglobinuria. It should be emphasized that the amounts of ascitic fluid administered to these animals were relatively large and would be equivalent to transfusions of 3,000 to 5,000 c.c. of ascitic fluid in man. Since the usual quantity of fluid transfused in man is only 500 to 1,000 c.c., it is obvious that the margin of safety is wide. No attempt was made to estimate the largest amount of fluid which could be tolerated.

*Transfusions of Incompatible Ascitic Fluid in Man.*—In order to complete this investigation, it was necessary to study the effect of the transfusion of incompatible ascitic fluid into human beings. The blood of the prospective human recipient was cross-matched with the ascitic fluid which was to be used for transfusion. The presence of definite agglutination of the red blood cells after incubation for forty-five minutes at 37° C. with the fluid was considered to be evidence of incompatibility. Using this criterion, six patients who were suffering from various minor forms of chronic infection were selected. The ascitic fluid after filtration was slowly heated to body temperature and administered by the intravenous route to each patient at a rate of 5 c.c. per minute. The amounts transfused varied from 200 to 415 c.c. A brief rigor occurred in two patients, while the other four patients showed no reaction (Table V). Upon blood examination, no evidences of agglutination were found in any of the subjects. Urinalysis revealed no albuminuria, hematuria, or hemoglobinuria. The ratio of the volume of ascitic fluid administered to the blood volume calculated from the body weight varied in four of the patients from 1:10.4 to 1:18.2 (Table V). In other words, the amount of fluid administered varied from 5 to 10 per cent of the calculated total blood volume. This is well within the limits of safety, inasmuch as in vitro studies have indicated that whole blood is capable of inactivating twice its own volume of ascitic fluid (Table II). The absence of agglutination in the blood of these patients after receiving incompatible ascitic fluid in quantities up to 415 c.c. suggests that the phenomenon of isoagglutinin inactivation occurs in vivo as well as in vitro.

#### COMMENT

It would seem pertinent at this point to discuss further the influence of temperature upon the inhibition of isoagglutinins. From the data al-

the greatest degree of inactivation of the isoagglutinins will occur if equal volumes of each fluid are used. It has been stated that the pooling of sera of differing groups will result in a serum which possesses an isoagglutinin titer lower than that of any of the individual sera present (Levinson and Cronheim<sup>25</sup>). Even better results, however, will be obtained if the pooling of the fluids is carried out with the volume factor in mind. By using equal amounts of antagonistic sera, it is possible to produce an isoagglutinin-inactivated fluid. This statement applies not only to simple Group A or B fluids, but also, as has been shown already, to Group O fluids which contain both a and b isoagglutinins. Of course, parallel results will be obtained if one uses plasma or ascitic fluid instead of serum, or mixtures of one with the other.

In discussing isoagglutinin inactivation *in vivo*, it should be remembered that most body tissues and fluids possess the power of absorbing group-specific isoagglutinins (Landsteiner and Levine,<sup>22</sup> Kritschewsky and Schwarzman,<sup>26</sup> Witebsky and Okabe<sup>27</sup>). However, since the concentration of group-specific substances varies in different tissues and body fluids (Schiff<sup>23</sup>), the ability of the latter to inactivate antagonistic isoagglutinins will likewise vary. The available sources for isoagglutinin inactivation are:

1. Plasma
  2. Cells
  3. Interstitial fluids
  4. Tissue cells
- } of blood

Since the process of agglutination may be completed in as short a time as thirty minutes and since a transfused fluid, such as plasma, serum, or ascitic fluid, will usually remain in the blood stream for periods longer than thirty minutes, it becomes apparent that, when the blood vessels are not abnormally permeable, the inactivation of incompatible isoagglutinins in the transfused fluid must take place to a major extent in the blood stream. Inasmuch as only a small amount of the transfused fluid passes into the extravascular spaces within thirty minutes, the tissue cells and interstitial fluids will play a minor role in the inactivation phenomenon. It has been shown (Table II) that both the cellular and fluid components of blood are capable of inactivating antagonistic isoagglutinins. A peculiar problem is presented by the fact that in those conditions in which plasma, serum, or ascitic fluid transfusions are indicated, namely, hemorrhage (loss of whole blood), trauma, burns (loss of plasma), and hypoproteinemia (loss of proteins), there occurs a reduction of those group-specific substances which are concerned with the process of inactivation of the isoagglutinins occurring in incompatible transfusion fluids. In hemorrhage the blood which remains in circulation is diluted by a fluid of low protein content which passes into it from the extravascular tissue spaces. In this way the isoagglutinin titer of the blood will be lowered, reducing its capacity

TABLE V

INFLUENCE OF TRANSFUSIONS OF INCOMPATIBLE ASCITIC FLUID INTO HUMAN RECIPIENTS

PATIENT	BLOOD GROUP	ASCITIC FLUID GROUP	CROSS-MATCHING TEST	CALCULATED BLOOD VOLUME (C.C.)	AMOUNT OF FLUID ADMINISTERED (C.C.)	VOLUME RATIO BLOOD-ASCITIC FLUID	RESULT
P. W.	A	B	Agglutination	4,648	300	15.4:1	No reaction
W. B.	A	B	Agglutination	3,652	200	18.2:1	No reaction
J. P.	A	B	Agglutination	4,482	415	10.8:1	No reaction
R. W.	B	O	Agglutination	2,622	259	10.4:1	No reaction
S. L.	B	O	Agglutination		275		Mild rigor
T. M.	A	O	Agglutination		325		Mild rigor

ready presented, there appears to be no doubt that such inactivation is greater at a temperature of 37° C. than at lower temperatures. Two possible explanations present themselves: (1) the isoagglutinin titers of biological fluids decrease as the temperature rises (Kettel<sup>24</sup>) and thus a fluid of naturally low isoagglutinin titer may fail to agglutinate sensitized red blood cells at higher temperatures; (2) the phenomenon of inactivation of isoagglutinins takes place more rapidly and more completely at higher temperatures. That the first explanation is inadequate is seen by the data presented in Table I. It will be noted that plasma, when diluted with an equal volume of isotonic sodium chloride solution in the control experiments, agglutinated group-opposite red blood cells at a temperature of 37° C. The same plasma, when mixed with group-opposite plasma under similar conditions of temperature and volume, showed definite inactivation of its isoagglutinins and failed to agglutinate group-opposite red blood cells. Since temperature plays such an important part in isoagglutinin inactivation, it is suggested that incompatible plasma, serum, or ascitic fluid be heated to body temperature before transfusion. The transfusion of cold incompatible biological fluids is, according to our experimental data, more apt to result in incomplete isoagglutinin suppression, with a resultant agglutination in vivo. Likewise, a rise in temperature of the blood of the recipient, as in fever, might be expected to accelerate the phenomenon of inactivation and, thereby, prevent agglutination in vivo after the transfusion of incompatible fluids.

It has been pointed out previously that the relative amounts of antagonistic fluids used influence the degree of isoagglutinin inactivation. While it is dangerous to generalize, one may be permitted to state that, when the isoagglutinin titers of any two biological fluids are unknown,



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to inactivate antagonistic isoagglutinins. In conditions in which the loss of plasma predominates, the high concentration of red blood cells will aid in isoagglutinin inactivation. Moreover, in such conditions there is present a localized area of increased vascular permeability at the site of trauma, through which a part of the transfused fluid with incompatible isoagglutinins will pass and there become inactivated. Frequently, however, a general increase in the permeability of the capillaries occurs and this will act as an additional safeguard by permitting the passage of part of the transfusion fluid into the interstitial tissue spaces, where further isoagglutinin suppression will take place. When the usual quantities of 500 to 1,000 c.c. of fluid are administered, these factors need not be considered, since there will remain in the blood stream sufficient group-specific substances to inactivate the incompatible isoagglutinins. However, when larger amounts of incompatible plasma, serum, or ascitic fluid are to be transfused, such factors merit consideration. Under these circumstances one may adopt one of three measures: (1) complete inactivation of the isoagglutinins in the plasma, serum, or ascitic fluid by mixture with an equal amount of a fluid of an opposite group; (2) partial inactivation of the isoagglutinins in the fluid by unequal pooling with fluids of an opposite and/or similar group; or (3) diminution of the titer of isoagglutinins by dilution of the fluid with isotonic sodium chloride solution. Finally, it should be noted that the process of isoagglutinin inactivation is completed rapidly in comparison with that of agglutination, and this provides a further safeguard in transfusions of incompatible plasma, serum, or ascitic fluid.

#### SUMMARY AND CONCLUSIONS

An investigation of the factors involved in the inactivation of isoagglutinins has been carried out by means of studies *in vitro* and *in vivo*. The importance of such factors as temperature and volume is emphasized. The transfusion of incompatible ascitic fluid into human beings is reported. The significance of these studies in relation to the general problem of transfusion of group-incompatible fluids into human beings is discussed.

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The investigation was carried out on fifty dogs, several procedures frequently being performed at various intervals on the same animal. The operations included gastroenterostomy, jejunoplasty, gastric resection and enteroanastomosis, etc. The animals were sacrificed at different periods following surgery and the anastomoses inspected grossly for the presence of infection, leak, free sutures, rigidity, and thickness of the anastomotic stoma. In each instance a careful record of the number, type, and anatomical position of all sutures, both absorbable and non-absorbable, was charted. On occasion the tracing of the sutures was facilitated by the use of a variety in color of the nonabsorbable suture material. After the animals were sacrificed, the circulation was washed out with saline solution and the vessels injected with colored gelatin mass. The majority of the specimens were rendered transparent by a modified Spalteholz technique. These transparent preparations enabled us to follow with considerable accuracy the fate, migration, and final

TABLE I

	STOMAL THICKNESS	BLOOD SUPPLY TO STOMA	EXPOSED SILK	PRESENCE OF ULCERS IN LUMEN
1. Continuous silk inner and outer layers	+++	Decreased	Always	Frequent
2. Continuous silk outer and continuous catgut inner layer	++	Adequate	Occasional	Infrequent
3. Interrupted silk outer and continuous catgut inner layer	+	Excellent	Rarely	None
4. Interrupted silk both layers	++	Adequate	Frequent	Rare
5. Interrupted catgut both layers	++	Excellent		Rare
6. Continuous catgut both layers	++	Adequate		None

position of the nonabsorbable suture material. By this clearing process the arteries and capillaries were traced with facility and an estimate of the adequacy of the circulation to the stomal area was readily made. Any silk suture which had become exposed in the lumen of the gut and subjected to digestive action rapidly lost color and in this way could be distinguished from those sutures buried in the tissues. In addition, material was removed from the stomal ring for histologic section and study.

## FINDINGS

1. *Continuous Silk in Both Inner and Outer Layers.*—The thickening of the stomal ring was maximal and the orifice was rigid and unyielding. The cleared preparations revealed a diminution in blood supply in the

# SILK

## ITS EFFECT AND FATE IN INTESTINAL ANASTOMOSIS

### AN EXPERIMENTAL STUDY\*

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AS a continuation of previous experimental investigations into the pressing problems of stomal obstruction and marginal ulcer in gastrointestinal anastomosis, we have been led to a study of those factors producing undue thickness, rigidity, and fibrosis of the anastomotic ring. Observations on our series of experimental animals early impressed us with the great variations of a structural and functional character found at the anastomosis. It became increasingly apparent, all other factors of surgical technique and procedure being equal, that the variable responsible for such differences was undoubtedly the type of suture material employed and the position occupied by this material. In those animals where both serosal and mucosal layers of a gastroenterostomy were done with continuous silk, a segment of this silk was invariably found extruded into the lumen of the gut. Under these conditions the stomal ring was always two to three times thicker than in those animals where silk was not used, or, if used, had not become exposed to the lumen. We concluded that this thickening was the result of the swelling, edema, and attendant fibrosis which followed infection.

Further, it was noted that as long as the silk remained partly within the tissue and partly exposed, the thickness persisted regardless of the number of days which had elapsed since operation. It was evident that in these cases the stoma was frequently so thick that the opening had little possibility of changing either in shape or size with peristalsis. It was decided, therefore, to investigate the reaction of silk and other suture material when employed in the following combinations in gastrointestinal surgery: (1) continuous silk in both the inner and outer layers, (2) continuous silk in the outer layer and continuous catgut in the inner layer, (3) interrupted silk in the outer layer and continuous catgut in the inner layer, (4) interrupted silk in both layers, (5) interrupted catgut in both layers, and (6) continuous catgut in both layers.

*Material and Methods.*—Much of the experimental data here presented was accumulated as a by-product of the study of the circulation of the stomach and jejunum following gastroenterostomy, jejunoplasty, or subtotal gastric resection on the dog.<sup>1</sup>

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Histologically the sections through the stoma showed a marked inflammatory reaction with a purulent exudate bathing the silk suture and in later stages an excessive fibroblastic reaction of poor quality and accompanying chronic inflammation. These changes were found constantly about the submucosal and not infrequently about the subserosal suture. The factors leading to infection of the subserosal suture are discussed below.

*2. Continuous Silk Outer Layer and Continuous Catgut Inner Layer.*—When continuous silk was used in the outer layer and continuous fine chromicized catgut in the inner layer, the thickness of the stoma was not excessive, provided the silk of the serosal layers did not become exposed within the lumen of the gut. However, if the continuous serosal suture became exposed in the lumen, as was not infrequently the case,



Fig. 3.—Submucosal catgut ten days postoperatively. Note beginning fragmentation and early invasion of cellular elements into the suture.

swelling, edema, and fibrosis occurred to almost the same degree as when both intestinal layers were closed with continuous silk. In a small series of experiments with this combination, the mucosal catgut suture was inserted deeply so as deliberately to pick up here and there the serosal silk suture. When this was done, the silk of the serosal stitch became invariably exposed within the lumen having been infected by the proximity of the mucosal stitch. A stoma of excessive thickness similar to that found in Group 1 above was produced. In like manner mucosal migration and infection of the serosal silk stitch took place when the suture was deliberately or accidentally inserted too deeply.

*3. Interrupted Silk Outer Layer, Continuous Catgut Inner Layer.*—There was seldom any increased stomal thickness, even though one or

region of the stoma. Histologic study showed that the thickening of the stoma and its diminished vascularity were due to the diffuse fibrous tissue reaction set up in all the intestinal layers along the infected pathway of the migrating silk sutures and that this reaction extended laterally for some distance from the line of anastomosis. Some silk was invariably found exposed, hanging festooned within the lumen, and small ulcers in the mucosa along the suture line were frequent.<sup>2</sup>



Fig. 1.—Suppuration surrounding interrupted silk suture which has migrated from the subserosal position.

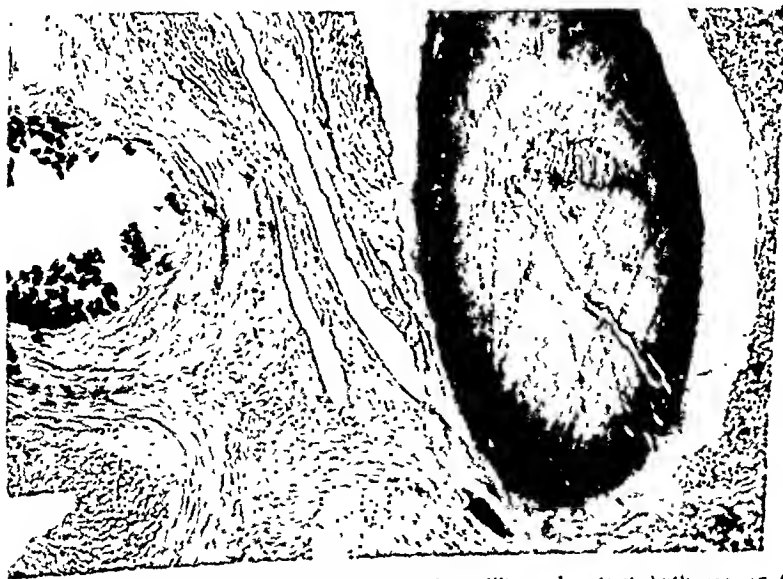


Fig. 2.—Animal fourteen days postoperatively. Silk and catgut both appear in same section. Note difference in degree of fibroblastic reaction about the two sutures. Silk suture surrounded by a much denser reaction.

4. *Interrupted Silk Sutures in Both Inner and Outer Layers.*—When the above combination was used, a satisfactory stomal ring of not undue thickness was encountered. It, however, was on the whole thicker than the combination used in Group 3. This, we feel, was due to the variation in the length of time it took the individual interrupted silk mucosal sutures to be cast off into the lumen. While they remained in place, they undoubtedly acted as a source of localized infection and in-



Fig. 5.—Sixteen-day-old catgut suture about to be cast off into the stomal lumen

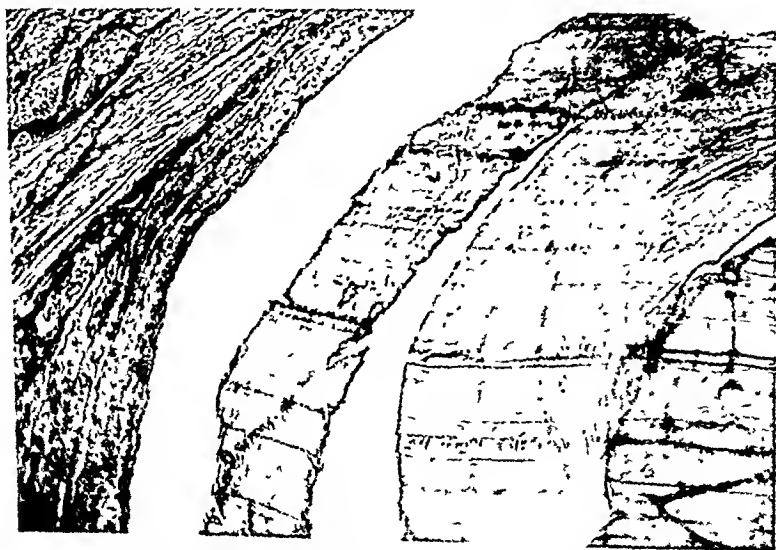


Fig. 6.—Interrupted catgut serosal suture. In absence of infection and with sub-serosal placement, it is surrounded by excellent fibroblastic response.

more of the individual silk sutures became exposed in the gut lumen. The blood supply to the stoma, as shown by the injected specimens, was invariably good. In all of nineteen such specimens little or no gross reaction at the suture line was found. Histologically any inflammatory reaction was confined to the submucosa, except where an individual silk suture had become exposed in the lumen. There was little or no fibrous tissue reaction except for that which occurred in the immediate proximity of the individually exposed silk suture. It was apparent that the inflammatory reaction which may follow the line of the small interrupted silk suture was confined to the course of the suture itself and did not extend beyond it. In addition such a suture when exposed was cast off very rapidly into the gut lumen. The time required for this extrusion varied from seven to sixty days but in the majority of cases was complete in fourteen days. It was clear that the inflammatory



Fig. 4.—Silk suture showing knot, placed deep into muscularis. Note excellent fibroblastic response and observe inflammatory elements.

process was markedly limited not only because of the small area involved but also by the short period of the inflammation terminated by the extrusion of the suture. The good results obtained with this combination emphasize two factors: (1) the time needed for casting off of the interrupted individual infected silk suture is short and (2) the limited area of inflammatory reaction is confined to the course of the individual silk suture. This is in contrast to the continuous silk suture which, when exposed in the gut, is attended by an inflammatory process over the entire stomal course which continues indefinitely until the whole suture has sloughed or rotted out.



Although it has not been our purpose to discuss the merits of silk versus catgut, our findings confirm those of numerous other observers; namely, that plain catgut excites a severe initial reaction and delays healing somewhat.<sup>4, 5</sup> Silk under like conditions and in like tissues produces a minimum reaction and healing is more rapid. Chromicized catgut in the smaller sizes lies midway between silk and plain catgut in degree of tissue reaction.

The experimental evidence points, therefore, to the unquestioned superiority of interrupted silk as the ideal suture material for the serosal layer in gastrointestinal surgery.

Our histologic preparations demonstrate clearly that there is a definite difference in fibroblastic reaction about both absorbable and nonabsorbable sutures, depending upon their location. Sutures lying in the serosa, subserosa, and muscularis are surrounded by a better quality of fibroblastic reaction. On the other hand, the reaction about sutures lying in the submucosa is invariably of poorer quality, characterized by immaturity of the fibroblastic elements and lack of density in the collagenous fibers. This suggests, apart from possible differences in tissue response in the various layers of the gut, a greater potentiality for infection due to the proximity of the infected lumen of the bowel.

It follows that the ideal suture for use in the submucosal and mucosal positions is continuous catgut, because all sutures in this position are necessarily more or less infected and catgut in the presence of infection undergoes early dissolution with a minimum of surrounding inflammation and fibrosis. The hemostatic qualities and the rapidity of insertion of a continuous suture are obvious additional advantages.

Finally, as a result of these experimental findings, the use of continuous silk and other continuous nonabsorbable suture materials has been discontinued in intestinal anastomosis at the University of California Hospital and the use of interrupted silk sutures substituted. In this connection, as long ago as 1902, Coffey<sup>b</sup> wrote: "I would eliminate the *continuous* Connell suture because it is more difficult to place at the end than an interrupted suture and remains hanging partially loose across the intestine for months after the operation, thus making at least a remote danger of obstruction. I would class the *interrupted* Connell suture as the ideal suture, the acme of surgical perfection, and as far as we may hope to go in intestinal anastomosis."

Interrupted silk on the peritoneal surface, placed to avoid as far as possible contact with the submucosal layer, together with continuous catgut on the mucosal aspect, is, in our opinion, the combination of choice for operations involving the anastomosis of the stomach to the small bowel and for enteroanastomosis. In the anastomoses of the large intestine, especially of the aseptic end-to-end type, two or more layers of interrupted silk can be used with less trauma and will give a firmer and safer union. Some of these sutures may eventually find their way into

flammation, thus contributing to the ultimate thickness of the stomal area. We noted, however, that it was the rule for these interrupted silk mucosal sutures to be cast off early, few of them remaining when the dogs were sacrificed at two to three weeks. With this method there was a moderate decrease in stomal circulation. There were only rarely any ulcers present along the suture line.

5. *Interrupted Catgut in Both Layers* and 6. *Continuous Catgut in Both Layers*.—When catgut sutures were used in both layers, whether continuous or interrupted, the healing was usually satisfactory and the stoma little or no thicker than in the other most favorable combination used in Group 3. There was no impairment of stomal circulation and stomal ulcers were not noted. We were definitely under the impression on gross examination of these anastomoses that it took longer for union to become firm and solid. This was confirmed by histologic examination, in which it was apparent that the quality of fibrous tissue reaction was inferior to that seen about an interrupted, uninfected silk suture.

#### DISCUSSION AND CONCLUSIONS

Our studies confirm the findings of Reichert and Holman (1925),<sup>1</sup> who showed that a suture has a tendency to migrate in the direction of its knot. However, this is only true provided the suture is uninfected, in which case it usually comes to occupy a position beneath the serosa. If infection supervenes, the suture will invariably migrate toward the lumen of the gut and eventually be cast off, regardless of the position of the knot.

These findings emphasize the necessity of using an interrupted suture so that, should it become infected, the individual suture alone will be cast off and tissue reaction minimized. Since every serosal suture which penetrates to the mucosa or even the submucosa is infected or potentially infected, great care should be taken in its placement so as not to carry it too deeply in the direction of the lumen. Should one bite of a continuous nonabsorbable suture become infected, the whole length of the suture becomes gradually involved and, as the infected suture works its way toward the lumen, the tissue reaction produced is maximal. Since the inflammatory infiltration accompanying the use of the combinations used in Groups 1 and 2 extended throughout the full thickness of the intestinal wall for some distance on either side of the anastomosis, it is possible that such an extensive infiltration may be a factor in the production of stomal and jejunal ulceration although experimental proof of this suggestion is wanting. In this regard the continuous catgut, because of its absorbability even when infected, is less objectionable than a continuous nonabsorbable suture. A continuous serosal suture, absorbable or nonabsorbable, however, for reasons stated above, does not rival the interrupted suture in the serosal layers.

## ABDOMINAL PAIN IN CYCLIC VOMITING

### ITS DIFFERENTIATION FROM ACUTE APPENDICITIS AND A RECOMMENDATION FOR ITS TREATMENT

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CYCLIC vomiting is a syndrome occurring in children. It is characterized by recurring attacks of vomiting, during which times there is an absolute intolerance for even fluid food, and is regularly accompanied by a marked ketonuria.

Cyclic vomiting generally occurs in children with some inherent tendency to a metabolic instability which is ordinarily not obvious but which may become activated by any one of many functional or organic disturbances. Overeating, excessive indulgence in fatty food, fatigue, excitement, an infection, upper respiratory, appendiceal or any other, may disturb the child so that vomiting starts. After vomiting for a variable period of time, the child may develop abdominal pain similar to that of diabetics with acidosis and often very much like that of an acute surgical abdomen.<sup>1, 2</sup>

The differential diagnosis in these conditions is difficult and becomes even more so because of the occasional simultaneous occurrence of recurrent vomiting and acute appendicitis. The differentiation between the abdominal symptoms of the diabetic ketosis and those of acute appendicitis have been dealt with quite adequately, especially by McKittrick,<sup>3</sup> who has summarized his conclusions as follows: "One is justified in saying that a history of malaise, drowsiness, vomiting, diffuse abdominal pain associated with widespread tenderness and spasm is so suggestive of diabetic acidosis, without demonstrable intra-abdominal pathology that operation should not be done unless the abdominal symptoms persist after three or four hours of adequate insulin treatment. Concisely, a history of abdominal pain with or without vomiting when associated with localized and definite abdominal tenderness, usually with spasm, is suggestive of a surgical lesion within the abdomen in the patient with diabetic acidosis, just as it is in the nondiabetic and may be an indication for immediate operation. In that rare case where definite differentiation is impossible and yet imperative, it may be safer to open the abdomen under local anesthesia than to suffer further delay."

While cyclic vomiting with abdominal symptoms presents a situation quite similar to that of diabetic ketosis, the basic conditions and their

the lumen of the gut and be cast off, but unlike catgut this does not occur until firm union has taken place. Those remaining and uninfected will eventually migrate to the subserous layer.

The experimental evidence indicates that, by utilizing the best features of both silk and catgut, the surgeon may attain more nearly to perfection in gastrointestinal surgery.

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TABLE II

DIFFERENTIATION BETWEEN ACUTE APPENDICITIS AND CYCLIC VOMITING WITH KETOSIS

	ACUTE APPENDICITIS	CYCLIC VOMITING WITH KETOSIS
Abdominal pain	Initial symptoms preceded by pain	Preceded by vomiting
Vomiting	Not recurrent	Reeurs often and at frequent intervals
Nausea	May persist	Persists
Temperature	Elevated	Elevated only with infection or dehydration
Pulse rate	Elevated	Elevated
Local tenderness	Present	Not usually
Muscle spasm	Present	Not usually
Leucocytosis	Moderate, occasionally normal	Moderate to marked
Ketonuria	May be present and severe	Always present
Respirations	Normal	May be rapid; later become deep
Blood sugar	Usually normal or hyperglycemia	Usually hypoglycemia
Response to antiketogenic therapy	Symptoms of appendicitis become more prominent	Symptoms disappear
Rectal examination	May be positive	Negative
Abdominal puncture	May be positive	Negative

Operation for appendectomy was ordered, but the attending pediatrician recommended that the ketosis be treated before surgical intervention was undertaken. Within thirty minutes following the intravenous administration of 400 c.c. of 5 per cent glucose in saline solution, improvement was almost phenomenal. The child sat up in bed and the abdominal tenderness disappeared completely. The temperature dropped to normal. The child continued to improve rapidly and he was discharged on Jan. 22.

One month later he was readmitted to the hospital because he had been vomiting repeatedly for twelve hours. Evidence of an acute upper respiratory infection was noted. The temperature was 103° and the pulse rate 126. An acetone odor was detected and acetonuria found. Adrenalin was injected subcutaneously in an attempt to cause rapid mobilization of sugar in his blood stream. The blood sugar immediately following this was 360 mg. per cent. Clinical improvement was noted following an infusion of 300 c.c. of 10 per cent glucose in saline solution. Three hours later the patient suddenly went into collapse, had a generalized convulsion, and despite intravenous glucose, oxygen inhalations, and stimulants, died. At post-mortem, death was found to be due to hemorrhage into the adrenals. The appendix was normal.

CASE 2.—(No. 414615.) E. M., a 3-year-old white boy, began to vomit on the evening of Sept. 26, 1937. The vomiting continued all through the night. At first this was bile stained and later became coffee-ground in appearance. A diagnosis of an acute surgical abdomen was made and hospitalization advised. On admission to the hospital the boy was acutely ill. The respirations were deep and a strong acetone odor was detected. His temperature was normal and the pulse rate was 120. The abdomen was scaphoid. Definite localized spasm was not present, but there was some resistance in the right lower quadrant. The remainder of the physical examination was negative. Acetonuria (three plus) was present. The white blood cell count was 16,800 with 81 per cent polymorphonuclear forms. The blood sugar was 75 mg. per cent; the urea was 42 mg. per cent, and the carbon dioxide com-

treatments differ sufficiently to warrant special consideration of the problem as it occurs in children with recurrent vomiting.

A group of cases have been selected which will best illustrate the problem and its management. While these cases are similar in many respects, they can be subdivided into three distinct groups

Group I consists of cases of cyclic vomiting associated with ketosis and abdominal symptoms suggestive of acute appendicitis. These patients may have a history of prior attacks or this episode may be the first of its kind. Group II consists of cases of acute appendicitis ushered in by repeated vomiting and occurring in children who are known to have had prior attacks of cyclic vomiting. Group III consists of those cases in which an attack of acute appendicitis is ushered in by repeated vomiting and in whom ketonuria is present. These patients have had no previous attacks of cyclic vomiting

TABLE I

## CLASSIFICATION OF TYPES OF CASES REPORTED

- 
- |   |
|---|
| I. <i>Cyclic Vomiting</i> —   |
| A. Initial attack or history of prior attacks of cyclic vomiting        |
| B. Present attack ushered in by repeated vomiting                       |
| C. Abdominal symptomatology simulating acute appendicitis               |
| D. Ketonuria  |
| E. No appendectomy  |
| II. <i>Acute Appendicitis With Recurrent Vomiting</i>                   |
| A. History of prior attacks of cyclic vomiting                          |
| B. Present attack ushered in by repeated vomiting                       |
| C. Abdominal symptomatology of acute appendicitis                       |
| D. Ketonuria  |
| E. Acute appendicitis at operation                                      |
| III. <i>Acute Appendicitis With First Attack of Repeated Vomiting</i> — |
| A. No history of prior attacks of cyclic vomiting                       |
| B. Present attack ushered in by repeated vomiting                       |
| C. Abdominal symptomatology of acute appendicitis                       |
| D. Ketonuria  |
| E. Acute appendicitis at operation                                      |
- 

## CASE REPORTS

CASE 1 — (No 262796) On Jan 4, 1926, C G, a 4 year old white boy, began to vomit. Vomiting continued hourly throughout the next twenty four hours, after which time he complained of diffuse abdominal pain. His physician made a diagnosis of acute perforated appendicitis and generalized peritonitis. On examination, the patient was semistuporous. His temperature was 101° and the pulse rate was 120. Breathing was deep and a definite acetone breath was detected. The abdomen was scaphoid and tender throughout. There was no evidence of localized muscle spasm and no rigidity. The white blood cell count was 13,000 with 78 per cent polymorphonuclear cells. The blood sugar was 140 mg per cent. Acetonuria was marked. The spinal fluid was entirely negative.



cent glucose solution were injected intravenously, followed by complete subsidence of all symptoms. The vomiting ceased and the child began to drink and eat. The temperature dropped to normal in twelve hours and there was no further abdominal pain. The boy made an uneventful recovery and was discharged as cured on June 1, 1939.

CASE 6.—(No. 390918.) K. S., a 15-year-old boy, had been well until Jan. 23, 1936, when he began to vomit and complain of abdominal pain. This continued through the night. The following morning his temperature was normal, but he was still complaining of abdominal pain. The abdomen was soft but distended. It was slightly tender generally, but there were no localized areas of tenderness or spasm. Rectal examination was negative. He had a marked acetone breath. On a regime of frequent small concentrated glucose feedings by mouth his condition improved so rapidly that he returned to school the following morning. He remained well for the next month, attending school regularly until Feb. 23, 1936 (nineteen days before admission to the hospital). At this time he again developed recurrent vomiting and abdominal pain associated with frequent loose watery stools, tenesmus, and a temperature of 102°. He was seen about twelve hours after the onset of vomiting and again placed on an antiketogenic regime which promptly corrected the vomiting. However, his pallor and very sick appearance, the abdominal pain, and tenesmus suggested a peritoneal irritation. The family refused hospitalization. Five per cent glucose in saline solution by intravenous infusion was given for several hours with striking but only temporary improvement. The temperature remained elevated and his general progress was slow. Hospitalization was again advised because of the suspected peritonitis but refused by the parents until March 13, 1936, at which time an abdominal mass was palpable externally and by rectum. On admission to the hospital the abdomen was moderately distended. Tenderness was elicited over the entire lower abdomen, especially on the right where a globular mass was palpable. A tender mass could be felt by rectum. The hemoglobin was 90 per cent with 4.6 million red blood cells and the white blood count was 28,200 with 86 per cent polymorphonuclear forms. A blood culture was sterile. At operation a large pelvic abscess was incised and drained. Culture of material from this abscess contained *Bacillus coli*. This surgical procedure resulted in only temporary relief. Signs of intestinal obstruction developed, necessitating colostomy. Following this the patient made a slow but progressive recovery.

*Comment.*—This case is important first, because no definite diagnosis was ever made; and next, because when the second attack of abdominal pain and vomiting occurred, the tendency was to delay surgical intervention or peritoneal aspiration on account of the very rapid improvement following the administration of glucose by mouth in the previous episode and the atypical gastrointestinal symptoms.

CASE 7.—(No. 415987.) R. P., an 8-year-old girl, was seen on Oct. 28, 1937, with a history of having had frequent attacks of cyclic vomiting with acetouria, one attack being severe enough to require relief through the use of glucose intravenously. Abdominal pain was usually associated with these episodes.

On Oct. 26, 1937, after a very large evening meal the child began to vomit and complained of abdominal pain. She was seen by her physician the following morning, who felt that this was another attack of cyclic vomiting. Nevertheless, he noted that in contrast to the previous episodes, she now had localized tenderness to the right of the midline in the lower quadrant. Rectal examination was negative and her temperature and pulse were normal. The child was given nothing but small

bining power 36.6 volumes per cent. Appendicitis or intestinal obstruction was suspected. A flat x-ray plate of the abdomen was negative.

The child was given a continuous infusion of 2,140 c.c. of 5 per cent glucose in saline solution over a period of forty hours. Within a few hours after the infusion was started, the abdominal signs completely disappeared. Recovery was uneventful and the child was discharged in excellent condition.

CASE 3.—(No. 379986.) J. S., a 6½-year-old girl, was first admitted to the Mount Sinai Hospital on Oct. 29, 1929, with a history of having had allergic eczema during infancy. At 5 years of age a tonsillectomy had been performed and was followed by recurrent vomiting. This was controlled by the administration of glucose by mouth. On Oct. 26 the patient had developed a mild upper respiratory infection accompanied by vomiting and severe abdominal pain. A diagnosis of acute appendicitis was made by the consulting surgeon and hospitalization advised. The temperature was 99.8° and the pulse rate 110. Just prior to her arrival in the hospital the child received a hypodermic injection of codeine which was followed by complete relief of all symptoms.

The patient was readmitted to the hospital on Feb. 24, 1930, having vomited for the three days prior to admission. Iced glucose solution by mouth was not retained. The vomiting was associated with severe cramplike abdominal pains which were generalized in character. The temperature was 100° and the pulse rate 132. Again a diagnosis of acute appendicitis was made. The child was almost moribund and dehydration was marked. There was some generalized but no well-localized area of tenderness, though abdominal pain was severe. The white blood cell count was 16,750 with 80 per cent polymorphonuclear cells and rose to 22,750 with 83 per cent polymorphonuclear cells that afternoon. The child was given two intravenous infusions of 350 c.c. of 5 per cent glucose in saline solution, each followed by temporary improvement. It was only after the use of the continuous infusion that a cure was obtained.

CASE 4.—(No. 439956.) C. P., a 6½-year-old boy, was seen on May 5, 1939, in his fifth attack of cyclic vomiting associated with severe abdominal pain. The first attack occurred at the age of 4½ years. This and the next three similar episodes were successfully treated at home. The fifth episode began the morning of admission to the hospital with vomiting, followed by severe cramplike abdominal pain and loose watery stools. On admission to the hospital, the pulse rate was 120 and the temperature 100.8. The fasting blood sugar was 100 mg. per 100 c.c. The urine contained acetone, 4 plus. The abdomen was quite soft and there was only slight right lower quadrant tenderness and no muscle spasm. Although surgery was advised, we decided to defer operation until the effect of antiketogenic therapy could be observed. After an intravenous injection of 5 per cent glucose in saline solution, the entire clinical picture cleared and the boy was discharged in excellent condition on May 27, 1939.

CASE 5.—(No. 440739.) K. B., an 8-year-old boy, was admitted to the Mount Sinai Hospital on May 20, 1939, because of headache, a temperature of 101°, persistent vomiting, and severe abdominal pain since May 17. The pain kept him awake at night. On May 20 a diagnosis of acute appendicitis was made and operation advised.

On admission to the hospital he was acutely ill. He was dyspneic and the temperature was 103.6°. The abdomen was soft, but slight tenderness was elicited to the left of the umbilicus. This was not severe and not well localized. The throat was moderately injected. Surgery was advised but was temporarily deferred because of the acute upper respiratory infection and ketosis. The white blood cell count was 18,900 and the acetoneuria was four plus. Twenty cubic centimeters of a 50 per

cent glucose solution were injected intravenously, followed by complete subsidence of all symptoms. The vomiting ceased and the child began to drink and eat. The temperature dropped to normal in twelve hours and there was no further abdominal pain. The boy made an uneventful recovery and was discharged as cured on June 1, 1939.

CASE 6—(No 390918) K S, a 15 year old boy, had been well until Jan. 23, 1936, when he began to vomit and complain of abdominal pain. This continued through the night. The following morning his temperature was normal, but he was still complaining of abdominal pain. The abdomen was soft but distended. It was slightly tender generally, but there were no localized areas of tenderness or spasm. Rectal examination was negative. He had a marked acetone breath. On a regime of frequent small concentrated glucose feedings by mouth his condition improved so rapidly that he returned to school the following morning. He remained well for the next month, attending school regularly until Feb 23, 1936 (nineteen days before admission to the hospital). At this time he again developed recurrent vomiting and abdominal pain associated with frequent loose watery stools, tenesmus, and a temperature of  $102^{\circ}$ . He was seen about twelve hours after the onset of vomiting and again placed on an antiketogenic regime which promptly corrected the vomiting. However, his pallor and very sick appearance, the abdominal pain, and tenesmus suggested a peritoneal irritation. The family refused hospitalization. Five per cent glucose in saline solution by intravenous infusion was given for several hours with striking but only temporary improvement. The temperature remained elevated and his general progress was slow. Hospitalization was again advised because of the suspected peritonitis but refused by the parents until March 13, 1936, at which time an abdominal mass was palpable externally and by rectum. On admission to the hospital the abdomen was moderately distended. Tenderness was elicited over the entire lower abdomen, especially on the right where a globular mass was palpable. A tender mass could be felt by rectum. The hemoglobin was 90 per cent with 4.6 million red blood cells and the white blood count was 28,200 with 86 per cent polymorphonuclear forms. A blood culture was sterile. At operation a large pelvic abscess was incised and drained. Culture of material from this abscess contained *Bacillus coli*. This surgical procedure resulted in only temporary relief. Signs of intestinal obstruction developed, necessitating colostomy. Following this the patient made a slow but progressive recovery.

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CASE 7—(No 415987) R P, an 8 year old girl, was seen on Oct 28, 1937, with a history of having had frequent attacks of cyclic vomiting with acetonuria, one attack being severe enough to require relief through the use of glucose intravenously. Abdominal pain was usually associated with these episodes.

On Oct 26, 1937, after a very large evening meal the child began to vomit and complained of abdominal pain. She was seen by her physician the following morning, who felt that this was another attack of cyclic vomiting. Nevertheless, he noted that in contrast to the previous episodes, she now had localized tenderness to the right of the midline in the lower quadrant. Rectal examination was negative and her temperature and pulse were normal. The child was given nothing but small

quantities of a glucose solution orally. Vomiting continued but at less frequent intervals. She was seen at 6:00 P.M. on Oct 27 and again at midnight. The tenderness and spontaneous pain continued, but there was no true rigidity and no fever. The child vomited almost every two hours during the night. On the morning of Oct. 28 the temperature was 100° and the pulse rate was 96. She had a mild glycosuria and severe acetoneuria. Abdominal pain continued and localized tenderness was more marked. In addition there was suggestive rebound tenderness. Because of the localizing signs a diagnosis of acute appendicitis was made and surgery advised. At operation a gangrenous appendix was removed, following which the patient made an uneventful recovery. The localizing signs became more evident only after the ketosis was treated.

CASE 8.—(No. 291130) J. C., a 4 year old girl, was seen on May 23, 1928, with a history of having been in good health until the night before, when she awoke from sleep and vomited. The vomiting recurred at frequent intervals through the night. She was seen at 8 o'clock the next morning and found to be in a semi-comatose state. The rectal temperature was 96° F., she was dehydrated and collapsed and the breathing was typically Kussmaul in character. The abdomen was scaphoid. There was no tenderness and no masses were palpable; however, on palpation over McBurney's area the right thigh became flexed on the abdomen. A rectal examination was done and was negative. One ounce every half hour of a mixture of one half orange juice and one half water with 10 per cent glucose was retained and the vomiting stopped. At noon the temperature was 98° and the child had abdominal pain. At 4:00 P.M. the temperature had risen to 104°. Abdominal pain was intense. The abdomen was distended and rigid throughout. Tenderness was generalized. Rectal examination revealed the presence of peritoneal fullness. The child was hospitalized immediately, at which time a white blood cell count was 7,000. At operation a gangrenous ruptured appendix was removed. Convalescence was uneventful.

*Comment.*—The child was in a state of semicoma and shock with hypothermia when first seen. It was only after the ketosis was treated and the circulation had improved that the abdominal signs and symptoms leading to the correct diagnosis became manifest. In retrospect, we believe that intravenous therapy might have been a more effective aid in arriving at the correct diagnosis more rapidly.

CASE 9.—(No. 402745) D. S., a 9 year old girl, was seen on Dec 26, 1936, with a history of having become nauseated and vomiting twenty four hours before admission. Vomiting became recurrent but was not associated with abdominal pain. Eight hours before admission the child was given a laxative which was followed by abdominal pain, severe enough to warrant hospitalization. On examination there was noted marked abdominal tenderness well localized in the right lower quadrant. The temperature was 103.6°. Urinalysis revealed a four plus acetoneuria. A continuous infusion of 5 per cent glucose in saline solution did not relieve the abdominal pain in two hours. An operation was therefore advised. A gangrenous appendix was removed and local peritonitis drained. The immediate postoperative course was very stormy. Ketoneuria persisted for four days postoperatively, even though a continuous glucose infusion was given during the entire time.

Perusal of the case histories and accompanying charts reveals several possible aids in differentiation between the cases of recurrent vomiting with and without appendicitis. Several of these findings deserve more detailed consideration.

# KARELITZ AND BLUMENTHAL: PAIN IN CYCLIC VOMITING

DIAGNOSIS OF FINDINGS IN CASES PRESENTED

GROUP	NAME	AGE	SEX	VOMITING	ABDOMINAL PAIN	TENDERNESS	TEMPERATURE	PULSE	W.B.C.	P.M.N.	KETO-NURIA	THERAPY	RESULT
I.	C. G.	1 yr.	M	36 hr., 20 hr.	General	General	101.0°	120	13,000	78%	3+	5% glucose in saline intra-venously	Improvement in 30 min.; no surgery
I.	L. M.	3 yr.	M	12 hr., recurrent	Right lower quadrant	General	99.0°	120	16,800	81%	2+	5% glucose in saline intra-venously	Improvement in few hours
I.	J. S.	6½ yr.	F	Recurrent	Severe, general; subsided with codeine	General	99.8°	110			3+		
				3 days	General	General	100.0°	132	16,750 22,750	80% 83%	4+	5% glucose in saline intra-venously	Improvement only after continuous infusion
I.	C. P.	6½ yr.	M	Recurrent, 6 hr.	General	None	100.8°	120	13,200	80%	4+	Glucose orally	Marked improvement
I.	K. B.	8 yr.	M	12 hr.	General	Left lower quadrant	103.6°		18,900		4+	20 c.c. 50% glucose intra-venously	Immediate improvement
II.	K. S.	15 yr.	M	Recurrent	Lower abdomen	Right lower quadrant	102.0°		28,200	86%	3+	Surgery	Appendical abscess
II.	R. P.	8 yr.	F	36 hr.	Right lower quadrant	Right lower quadrant	98.6°	96			4+	Surgery	Gangrenous appendix
III.	J. C.	4 yr.	F	12 hr.	None	General	96.0° 104.0°		7,000		4+	Surgery	Ruptured appendix
III.	D. S.	9 yr.	F	24 hr.	Right lower	Right lower	103.6°	120					

*Vomiting.*—In acute appendicitis vomiting usually follows the onset of pain and generally occurs only once or twice unless peritonitis is present. The vomiting may reveal food which was ingested a considerable period before, indicating the presence of pylorospasm. If vomiting occurs in a child with a history of, or a tendency to, cyclic vomiting, it may recur as was noted in the cases of Group II or III. Cyclic vomiting usually precedes the abdominal pain. Once the vomiting has started, it is repeated frequently and may continue day and night for one to three days and sometimes longer. During the attack, any intake of food or fluid, even small sips of water, may be sufficient stimulus for vomiting. The vomitus becomes bile stained and if it continues long enough, may contain blood.

*Abdominal Pain and Tenderness.*—The abdominal pain of cyclic vomiting and ketosis is most often generalized in character, but it may be upper abdominal at the onset with later localization to the right lower quadrant. Abdominal tenderness is usually absent early, but becomes a factor as the vomiting continues. The pain and tenderness are occasionally excruciating (Case 4). Although there may be greater intensity of the tenderness in the right lower quadrant, it is usually widespread and rarely well localized. This is in marked contrast to those cases of acute appendicitis which begin with recurrent vomiting. There develops abdominal tenderness localized to the right lower quadrant which is persistent. In general when the abdominal symptoms of ketosis are severe, the picture is usually more like that of a widespread generalized peritonitis than that of a localized inflammatory process. The absence of well-localized abdominal tenderness is one of the most consistent features of ketosis.

*Fever.*—Fever is usually present in acute appendicitis and absent in cyclic vomiting. This is, however, not always so. Acute gangrenous appendicitis may occur with little or no fever (Cases 7 and 10). Cyclic vomiting may be accompanied by fever when there is also present infection which commonly initiates the attack (Case 5) or it may result from the dehydration which follows repeated vomiting and starvation (Case 1). Under such conditions the temperature may be very high. In Case 8 the acidosis and shock were so profound that the temperature was abnormally low (96° F. rectally) and only became elevated following antiketogenic therapy.

*Pulse.*—The pulse rate is usually accelerated in acute appendicitis even without fever. It is also accelerated during the acidotic stage of cyclic vomiting. In ketosis without appendicitis the pulse tends to return to normal after treatment; whereas, it continues to be rapid, if inflammation of the appendix is present.

*Respirations.*—In cyclic vomiting the respiratory rate is influenced by the temperature and even to a greater degree by the ketosis and toxemia. Increase in rate to 60 or 80 respirations per minute may be observed.

Perhaps of greater importance than the rate itself is the character of the respiratory excursions. They are usually deeper and at times Kussmaul in character. In the presence of acute appendicitis the respirations are increased along with the fever, but they may be altered by splinting of the right side of the abdomen. In cyclic vomiting splinting is not commonly a factor.

*White Blood Count.*—The white blood cell count in nondiabetic as in diabetic ketosis is characterized by leucocytosis, sometimes of a very marked degree. It may reach 50,000 with a high percentage of polymorphonuclear forms. It is more common for a white blood cell count of 5,000 to 10,000 to be associated with acute appendicitis than with ketosis (Case 8).

*Rectal Examination.*—The rectal examination may be informative in the differential diagnosis in the presence of a gangrenous appendix, an appendical abscess, or peritonitis when fullness or tenderness usually is elicited in the right lower quadrant. In cyclic vomiting the rectal examination is negative.

#### DISCUSSION

When an attack of cyclic vomiting has been established, ketonuria and ketonemia, a low fasting blood sugar,<sup>4</sup> and a glucose tolerance response<sup>5</sup> similar to that of the diabetic are usually noted. Dehydration ensues and occasionally circulatory collapse results. In most instances a glycogenic substance, e.g., glucose, will terminate the acute attack. The commonly observed pylorospasm manifested by the vomiting of food ingested many hours before the onset of symptoms and the early appearance of ketones in the urine seem to indicate that in both conditions, cyclic vomiting and acute appendicitis, starvation may have existed previous to the manifestation of the illness. This starvation causes a depletion of liver carbohydrate followed by an increased tendency to burn fat and the production of ketosis.<sup>6-8</sup>

In all the cases of cyclic vomiting and appendicitis presented, ketonuria was consistently noted. Many of the patients had acetone breath, while some manifested typical Kussmaul breathing. The ketonuria persisted in some for several days after treatment was started even though the clinical improvement was rapid. In Cases 1, 7, and 8 the ketosis was profound and was accompanied by a state of semicomatose and of a very severe circulatory disturbance. During this severe state, the abdominal symptoms of Case 8 were completely masked and the rectal temperature was 96° F. Only when the dehydration and ketosis were treated did it become evident that our patient had an acute abdomen. McKittrick made a similar observation in some of his diabetics.

Several cases of gangrenous appendicitis had glycosuria and hyperglycemia, as well as ketonuria. These findings were so severe in some instances as to require insulin. In each instance spontaneous correction of this metabolic disturbance followed within seven to fourteen days.

The metabolic disturbance here resembled that of a temporary pancreatic dysfunction, possibly an insulin insufficiency secondary to infection.

It has already been noted that in both the cases of cyclic vomiting with abdominal symptoms as well as those of acute appendicitis with recurrent vomiting there is evidence of altered carbohydrate metabolism, ketosis, dehydration, and in some instances circulatory disturbances. Diabetics in impending coma who commonly present a similar picture are relieved of their abdominal pain when the dehydration and the altered circulation are treated by the administration of fluids, glucose and insulin. While glucose, salt, and fluid are necessary, the low blood sugar commonly noted in the cases of cyclic vomiting contraindicates the use of insulin. The abdominal pain of cyclic vomiting as well as the vomiting itself usually respond to the administration of a glycogenic substance such as glucose. It seemed reasonable therefore to utilize this approach as a possible aid in diagnosis in those cases which could not easily be differentiated by their presenting signs and symptoms.

The method of administering this therapy is dependent on several factors. Since vomiting is so prominent a feature, the oral administration of glucose solution is usually inadvisable. Even if effective the response to oral therapy may be too slow. In view of the abdominal symptoms rectal instillation of fluid would seem to be unwarranted. A single intravenous injection of glucose is often sufficient to correct the condition, but the abdominal symptoms may recur, necessitating the repetition of the injection as in Case 3. The form of treatment which we have found to be most effective is the continuous intravenous administration of 5 per cent glucose in Ringer's or Hartmann's solution for one to three hours, or longer as indicated. By this procedure, fluid, minerals, and glucose are supplied. The dehydration is controlled, the shock and collapse are eliminated, and the production of ketone bodies is inhibited. In addition, glucose is supplied perhaps for immediate consumption as well as for the glycogen-poor liver.

In the cases treated it was noted that after intravenous glucose and saline solutions were injected, correction of the abdominal pain, vomiting, fever, and tachycardia usually followed rapidly in the cases of cyclic vomiting. The respiratory rate changed. The increased white blood cell count fell toward normal. Contrasted to this in acute appendicitis after intravenous fluid therapy, the ketosis was only diminished. The white blood count did not drop appreciably and the abdominal signs and symptoms of acute appendicitis became more definite. Thus the indication for surgery became established. If the question was one of generalized peritonitis, an abdominal puncture was done as a diagnostic aid.

#### SUMMARY

A series of cases has been presented, all of the cases having several common factors. The patients had vomited many times in a short in-



terval; they had abdominal pain, leucocytosis, tachycardia, fever, and ketonuria. Surgery for appendicitis had been advised in all but one instance. Some of these were cases of cyclic vomiting, while others were acute appendicitis. Careful evaluation of the history and of the signs and symptoms was usually adequate for a diagnosis. When a definite diagnosis could not be made, antiketogenic and hydration therapy were found to be of valuable diagnostic aid. Operation was performed only when the proper indications had been established.

The intravenous injection of a glucose and salt solution is simple and safe and effective and was found to be the procedure of choice in the rapid treatment of ketosis. This improved the general condition of the patient, so that if surgery became necessary, the patient was a better risk. We therefore recommend the therapy as suggested to be employed in all cases presenting this diagnostic problem.

#### CONCLUSIONS

1. Cyclic vomiting is often accompanied by acute abdominal symptoms resembling those of appendicitis.

2. Acute appendicitis may begin with recurrent vomiting in children who have, as well as in children who have not, had prior attacks of cyclic vomiting.

3. The symptoms of acute appendicitis may be masked by the ketosis and become manifest only after correction of the ketosis and disturbed circulation.

4. Ketonuria is often present in children with acute appendicitis even though the history is of short duration.

5. Antiketogenic therapy clarifies the clinical picture. In cases of cyclic vomiting the abdominal discomfort and tenderness become less and the fever and leucocytosis diminish; whereas, in acute appendicitis the abdominal symptoms become more distinct, the tenderness persists and becomes more localized, the fever, tachycardia, and leucocytosis continue.

6. In all cases in which the differential diagnosis between acute appendicitis and abdominal pain associated with ketosis and recurrent vomiting is obscure, treatment of the ketosis and deranged circulation by continuous intravenous administration of a glucose containing saline fluid is recommended until the correct diagnosis becomes clear.

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# THE TREATMENT OF INGUINAL HERNIA BY INJECTIONS UNDER OPERATIVE VISUALIZATION

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THE number and variety of operative procedures advocated for the treatment of direct inguinal hernia comprise clear evidence of the lack of uniformity and satisfactory results in its surgical therapy. Andrews and Bissell<sup>1</sup> collected the results of 1,545 operations for direct inguinal hernia by different surgeons and reported an average recurrence rate of 20 per cent. In view of the foregoing, the application of still another method in the treatment of direct inguinal hernia appeared to us to be worthy of consideration.

According to the experience of the proponents of the injection treatment of hernia, this form of therapy is most suitable for small, reducible, indirect inguinal hernias in young patients with good tissues. It seemed illogical to us to apply the injection method in such cases because of the good results of surgery which are usually obtained and the difficulties and prolonged period of the injection treatment. On the other hand, a proper field for the injection treatment might exist in the problem of direct inguinal hernia because of the uncertainties of operative results. Accordingly we determined to try the method in cases of direct inguinal hernia including recurrent hernia.

Up to the present time objections to the injection treatment of direct inguinal hernia have been the poor results obtained, the prolonged period of treatment, and the possibility of injury to the cord structures and entry of the peritoneal cavity. Although accidents are rarely reported, there have been three fatal cases of perforation of the intestine resulting in peritonitis (Berne<sup>2</sup> and McKinney<sup>3</sup>).

In order to attempt to evaluate the results of the injection treatment with some degree of precision and also to obviate the dangers from and the prolonged application of the method, we determined to employ the method under visualization. Accordingly the plan was to inject a sclerosing solution into selected tissues through an open wound. The method employed was as follows: Under local anesthesia, an incision about two inches long was made in the lower third of the inguinal canal. The aponeurosis of the external oblique was exposed. In some cases in which the external ring was wide and thinned out, the sac of the direct hernia could be visualized without division of the aponeurosis. In most cases the aponeurosis was incised over the site of the hernial sac. The material injected was sylnasol, a 5 per cent solution of a vegetable oil extracted

from psyllium seeds. From 20 to 50 c.c. were injected into the peritoneal tissues over the dome of the sac and between the transversalis fascia and the adjacent sac. In this way the injected material was placed directly in the region in which fibrosis might effect a cure of the hernia. If the external oblique aponeurosis was incised, it was closed with a few catgut sutures, followed by skin closure. The patient was fitted with a truss before being allowed out of bed and was instructed to wear the truss for a period of one year.

At operation there was always noted an immediate bluish discoloration of the injected tissues. The injections produced no discomfort. There was fever after the injections in all cases, usually persisting for a few days. In most cases the wounds healed by primary union, but, in a few instances in which larger amounts of the sclerosing fluid were used, there were collections of serum in the wounds or infections. No other untoward effects were noted. The following is an analysis of our experiences with the method that has been outlined.

*Direct Inguinal Hernia.*—There were 17 cases of direct inguinal hernia. Eight patients were more than 50 years of age, the average age being 48 years. The duration of the hernias varied greatly, the average period being eight years. Most of the patients were obese with protuberant abdominal walls. They were selected for treatment by injection because they were regarded as not offering a favorable outlook for cure by operative treatment.

At the time of the injection a record was made of the size of the hernial sac. The average was 6 cm. in length and 4 cm. in width. From 20 to 50 c.c. of the sclerosing fluid were used, the average being 30 c.c. In 5 cases the external oblique aponeurosis was not opened, in 4 cases it was opened for a short distance, and in 8 cases it was opened the length of the inguinal canal.

The highest average temperature after injection was 101.8° and the average duration of fever was four days. In 11 cases healing was by primary union and in 4 there were collections of serum which did not interfere with healing. There were 2 infections. On an average the patients were out of bed on the seventh day and were discharged from the hospital on the tenth day after injection.

All of the patients were examined at regular intervals at follow-up. Although we stressed the importance of the continuous wearing of trusses, we found that only 6 patients wore them continuously for a year. Sixteen patients were followed for more than one year, the longest follow-up period being thirty-three months. In this group there were 10 cures and 6 recurrences, a recurrence rate of 37 per cent. Five of the 6 patients who wore trusses continuously for a year were well. If we consider as cured only those patients who were free of recurrences after having discarded trusses for more than six months, 8 patients (50 per cent) can be so classified. The patients without recurrences were fol-

lowed for an average period of twenty-two months and had not worn trusses for an average period of fourteen months. Five of the 6 recurrences occurred within sixteen months after injections. There were recurrences in both patients in whom infection of the wound had occurred. In 1 patient in whom follow-up was lost after six months there was no recurrence at the time of the last examination.

In addition to this group of direct inguinal hernias, there was 1 case of large direct and indirect inguinal hernia. The patient was 60 years of age and wore his truss for five months after injection. A recurrence was noted sixteen months after injection.

*Recurrent Direct Inguinal Hernia.*—There were 3 patients with recurrent direct inguinal hernia. Two patients were more than 50 years of age. In 1 case the hernia was twice recurrent after operation. This patient was a poor operative risk with hypertension, emphysema, and obesity. In all 3 cases the hernial sacs were large, averaging 8 cm. in length and 5 cm. in width. An average of 45 c.c. of sclerosing fluid was used. The highest average temperature after injection was 102° and the duration of fever, six days. In the first case the wound healed by primary union; in the second there was a collection of serum which did not interfere with healing; and in the third case infection of the wound occurred.

Two patients wore trusses continuously for six months, and 1 for ten months. All were followed for more than one year, the longest follow-up period being thirty months. None occurred in the case with the longest follow-up, the truss having been discontinued for twenty months. In the other 2 cases recurrences took place after one year.

*Combination of Injection and Hernioplasty.*—An attempt was made to modify further the injection treatment by combining operation with injection in cases of combined indirect and direct inguinal hernia. The procedure consisted in excision of the indirect sac, injection of the direct hernia as previously outlined, and repair of the inguinal canal. This was carried out in 4 patients. The average age was 52 years. The hernias were large in all cases, extending into the scrotum. After operation trusses were worn for one year in 2 cases and were not worn in the other 2 cases. All were followed for more than one year, the longest period being twenty-five months. Three patients were well. The fourth had a recurrence which at reoperation proved to be a recurrence of the indirect hernia with no evidence of recurrence of the direct hernia. This patient wore his truss for one year.

In addition to the foregoing group, there was 1 case in which the indirect sac was excised and the direct hernia injected without repair of the inguinal canal. This patient did not wear a truss and was well thirty months after treatment.

The combination of injection and operation was used in 2 cases of recurrent direct inguinal hernia. One patient wore a truss for three

months and was well twenty-three months after the operation. The other patient did not wear a truss and there was a recurrence ten months after operation.

*Histologic Studies.*—The effects on tissues of injections of the extract of psyllium seeds have been reported. Rice<sup>9</sup> noted an inflammatory exudate of polymorphonuclear leucocytes and few connective tissue cells in dogs in sections obtained fifteen hours after injections of the muscle.

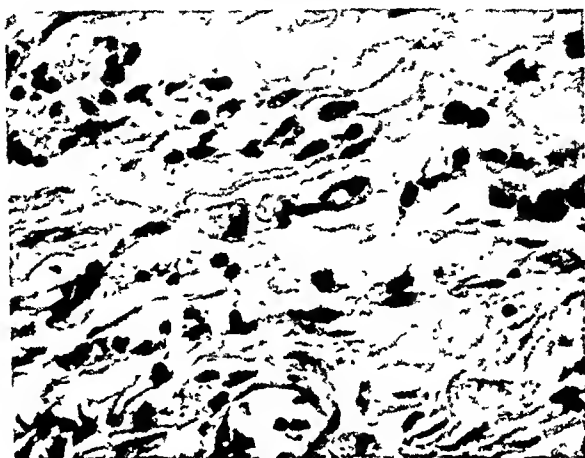


Fig. 1.—Section one month after injection showing loose fibrous tissue containing lymphocytes and pigment-bearing histiocytes ( $\times 650$ ).

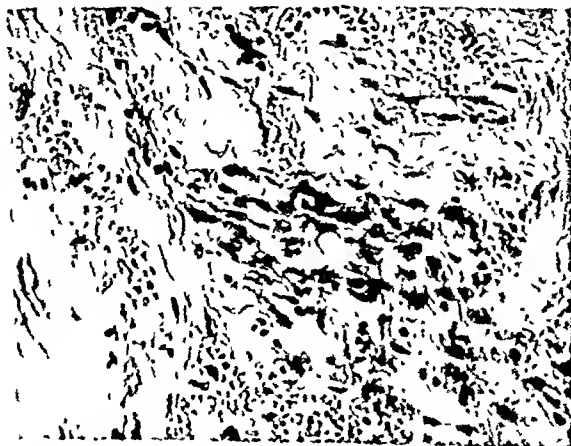


Fig. 2.—Section two months after injection showing more compact fibrous tissue with a group of pigment cells ( $\times 100$ ).

Sections made after longer periods revealed a reaction of fibroblasts with a gradual change into mature fibrous tissue in from eighteen to forty-two days.

Manoil<sup>1</sup> injected the abdominal wall of rats with 0.15 to 0.5 c.c. of sylvadol and made sections at intervals of one hour, one and three days,

and one, two, three, four, six, and eight weeks after injection. The sections one day after injection showed an acute inflammatory exudate of polymorphonuclear leucocytes. Large numbers of fibroblasts were noted from the third day to the fourth week. There was slight necrosis three weeks after injection. Beginning fibrosis, noted one week after injection, became marked in six and eight weeks.

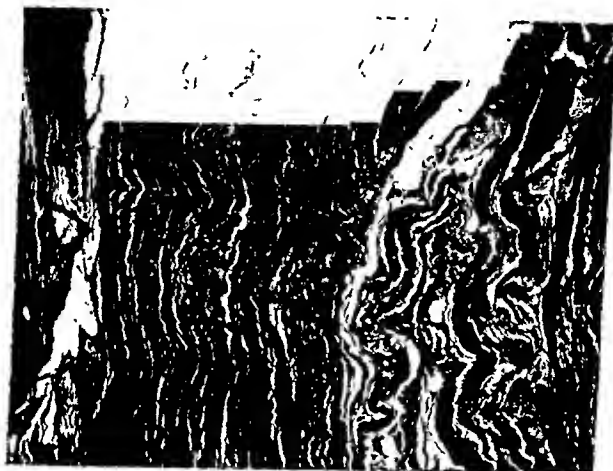


Fig. 3.—Section four months after injection showing dense bands of compact fibrous tissue ( $\times 90$ ).



Fig. 4.—Section six months after injection showing bundles of fibrous tissue separated by fat ( $\times 62$ ).

Similar results were reported by Dobson<sup>4</sup> after injections of psyllium seed extract into the rectus muscle of dogs. This report is important in that studies were made as long as ten months after injection. The latter showed that in place of the diffuse sheets of fibrous tissue noted during the first four months the fibrous tissue generally appeared as small islands in the later sections.

Experimental injections in dogs were carried out by one of us (E. E. A.) using the same material, psyllium seed extract, and the same method employed as in the treatment of patients. Six one-inch incisions were made in the skin of the backs of dogs, and 5 c.c. of sylnasol were injected into the subcutaneous tissues, fascia, and musculature of the back. Sections of the injected tissues were made at monthly intervals for a period of six months after injections. We are indebted to Dr. Abou D. Pollack for the histologic examination of the specimens.

Sections one month after injection (Fig. 1) showed numerous small cystic spaces lined by dark, flattened cells. The surrounding fibrous tissue contained lymphocytes and histiocytes, the latter holding yellow pigment. After two months (Fig. 2) there were large areas of fibrosis containing pigment cells which tended to accumulate around vessels and also areas of lymphocytic infiltration. After four months (Fig. 3) there was marked fibrosis with dense bands containing pigment. Sections six months after injection (Fig. 4) showed that these bands were not continuous but assumed a nodular arrangement. The fat tissue between the fibrous bundles was rather loose.

*Operative Findings in Previously Injected Hernias.*—Burdick and Coley<sup>3</sup> reported the findings in 8 patients treated by injections in whom subsequent operations were performed. They stated that "in no case did we find the clinical or microscopic evidence of a strong bulwark of built-up scar tissue." We had the opportunity to observe the injected tissues of 3 patients operated upon after recurrences following injections. The appearance of the previously injected tissues made possible an evaluation of the tissue changes induced by the injections.

In the first case 20 c.c. of sylnasol were injected in a patient with a direct inguinal hernia. A recurrence was noted ten months later. At operation at that time a moderate amount of fibrous tissue was encountered subcutaneously. The sac was free from scar tissue. The second case was one of direct inguinal hernia. Forty cubic centimeters of sylnasol were injected. The hernia recurred one year after injection and operation was performed at that time. The findings were similar to the first case, a moderate amount of fibrosis in the subcutaneous tissues, but none about the sac. There was a large indirect and direct inguinal hernia in the third case. The treatment was a combination of hernioplasty and injection; excision of the indirect sac, injection of the direct component, and repair of the inguinal canal. Fifty cubic centimeters of sylnasol were injected. A recurrence was noted fourteen months later. Operation was performed eighteen months after the original operation. The recurrence was found to be an indirect hernia with no evidence of a direct sac. There was little fibrosis in the inguinal canal.

#### COMMENT

The tissue changes induced by injection of the psyllium seed extract are those of inflammation and repair induced by a chemical irritant. The

efficacy of the injection treatment of hernia depends upon whether or not fibrosis is complete and permanent enough in order to effect a cure.

The numerous publications on the injection treatment of hernia are contradictory in their estimation of end-results. If these results are to be evaluated, reliance can be placed only on reports based on personal follow-up examinations.

In a group of 300 cases reported by McKinney,<sup>8</sup> 230 patients were personally examined and 70 patients replied by letter or were examined by other physicians. Six months' time had elapsed from the date of the last injection before examination in all cases and in the majority from one to three and one-half years. There were cures in 83 per cent of the cases. Using similar criteria for cure, Rice<sup>10</sup> reported 97.6 per cent cures in 456 cases of inguinal hernia. Harris and White<sup>5</sup> reviewed 236 cases of inguinal hernia in which 57 per cent of the patients were well six months to three years after the removal of trusses. Of the remainder, 28 per cent were still wearing trusses and 15 per cent were not cured.

In direct contrast to these favorable results, Burdick and Coley<sup>3</sup> reported a recurrence rate of 81 per cent in a group of 56 cases of inguinal hernia. Slater<sup>11</sup> followed a group of 20 patients who had received courses of injections for inguinal hernia. All had been considered cured at the completion of the treatment. The follow-up study was begun two years after the first injection and extended into the fourth year. Recurrences were noted in 4 cases two and one-half years after the first injection. The number of recurrences increased so that at four years there were only 2 patients free from recurrences.

Dobson<sup>4</sup> reported follow-up studies in patients from six months to two and one-half years after removal of trusses. The cases included 53 indirect inguinal, 19 direct inguinal, and 6 recurrent inguinal hernias. Recurrences were noted in 37.7 per cent of the indirect inguinal hernias, 68.4 per cent of the direct inguinal hernias, and in all of the recurrent hernias. Manoil<sup>7</sup> reviewed a group of 158 hernias of all varieties treated by injections. There were recurrences in 19.6 per cent of the cases, but 29 per cent of the patients were still wearing trusses.

The results obtained in our cases have not been satisfactory despite the fact that injections were made under vision precisely in the region in which fibrosis would be desired to effect cure. A study of the sections made from animal experiments suggests that the reasons for poor results are the incompleteness and impermanence of the fibrosis. Our experience with recurrences operated upon after injection treatment establishes that relatively little fibrosis existed at the sites of injection.

#### SUMMARY\*

Injections under operative visualization were used in the treatment of direct and recurrent inguinal hernias and in conjunction with hernio-



plasties in combined indirect and direct inguinal hernias. Large amounts of psyllium seed extract were injected into the properitoneal tissues over the hernial sacs and between the transversalis fascia and the adjacent sacs. Trusses were worn in most cases following injections.

There were seventeen cases of direct inguinal hernia treated in this way. Sixteen patients were followed for more than one year, the longest follow-up period being thirty-three months. There were 10 cures and 6 recurrences, a recurrence rate of 37 per cent. Eight patients (50 per cent) were well after discontinuance of trusses for more than six months. The patients without recurrences were followed for an average period of twenty-two months and had not worn trusses for an average period of fourteen months.

Three patients with recurrent direct inguinal hernias were treated. All were followed for more than one year, the longest follow-up period being thirty months. There were recurrences in 2 cases. The third was well thirty months after injection and had not worn a truss for twenty months.

In 5 patients with combined indirect and direct inguinal hernias, the indirect sacs were excised, the direct hernias injected, and the inguinal canals repaired. All patients were followed for more than one year, the longest period being twenty-five months. Four patients were well; the fifth had a recurrence of the indirect hernia. Two patients with recurrent direct inguinal hernias were treated by combined injections and hernioplasties. One was well twenty-three months after operation; the other had a recurrence in ten months.

Following injections of psyllium seed extract in dogs, there was only incomplete production of fibrosis. Observations of patients operated upon after recurrences following injections failed to reveal adequate fibrosis.

Since this report the results of further examinations of these patients, the most recent in September, 1941, are as follows:

In the group of 16 patients with direct inguinal hernia followed for more than one year there were 9 cures and 7 recurrences, 43.7 per cent recurrence rate; the longest follow-up period was three years and nine months. The patients without recurrences were followed for an average period of two years and four months and had not worn trusses for an average period of one year and six months. One patient with a recurrent direct inguinal hernia has remained well for three years and three months, the truss having been discontinued for two years and five months. Four patients with combined indirect and direct inguinal hernia treated by injection and hernioplasty have remained well for more than two years, the longest follow-up period being three years and three months.

## CONCLUSION

Although injections under operative visualization have cured cases of inguinal hernia not suitable for cure by operation, the method has proved to be too uncertain in results to be advocated as a dependable therapeutic procedure.

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# SIMPLIFIED TECHNIQUE FOR AMPUTATION THROUGH THE THIGH

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THE technique to be described is intended for amputations through the muscular portion of the thigh, usually about the lower or middle third. Its execution obviates the necessity of elevating, turning, or twisting the extremity in order to expose the posterior surface or the great blood vessels and avoids the unsurgical appearance, disarrangement of drapings, and frequent contamination which such maneuvering engenders.

The operation embodies rapidity, simplicity, a minimum of assistance, and, we believe, sound surgical principles.

The technique is as follows:

The thigh is scrubbed thoroughly with soapsuds and cleansed with alcohol. A large sterile sheet is placed under the extremity to well above the operative site. Another sheet is placed over the leg to just above the knee and here fixed securely. A third sheet covers the patient's body to the upper end of the first sheet, to which it is fastened securely and snugly about the thigh. A large block of sterilized cork is placed beneath the thigh at the level of the operative site. No tourniquet around the thigh is used.

Any gaseous anesthetic is satisfactory. We have not found spinal anesthesia necessary.

A sweeping, slightly curved anterior flap is made, the incision extending at once down to the femur. The soft tissues at the sides of the bone are easily pushed posteriorly, and the scalpel is run for a distance along the linea aspera to free the attachments of the adductor muscles.

A flat band retractor is inserted through the upper portion of this tunnel, and at this point, the femur is at once sawed through. The band acts as a guard against injury to the underlying tissues.

A tape is placed around the distal fragment which is strongly elevated by the assistant. Downward pressure exerted upon the band compresses the vessels in the posterior flap against the cork block, thus acting as a temporary tourniquet. The vessels now may be easily picked up with hemostats under direct vision, or the posterior flap may immediately be made by cutting across from above downward; that is, from beneath the distal fragment down upon the cork block.

The severed extremity need not be removed from the operating table, since it remains under the sterile sheet and does not interfere with the succeeding steps of the procedure.

The thigh is flexed so that the cut surface points ceilingward. The vessels are ligated, nerves cut short, and the bone end trimmed as the surgeon desires.

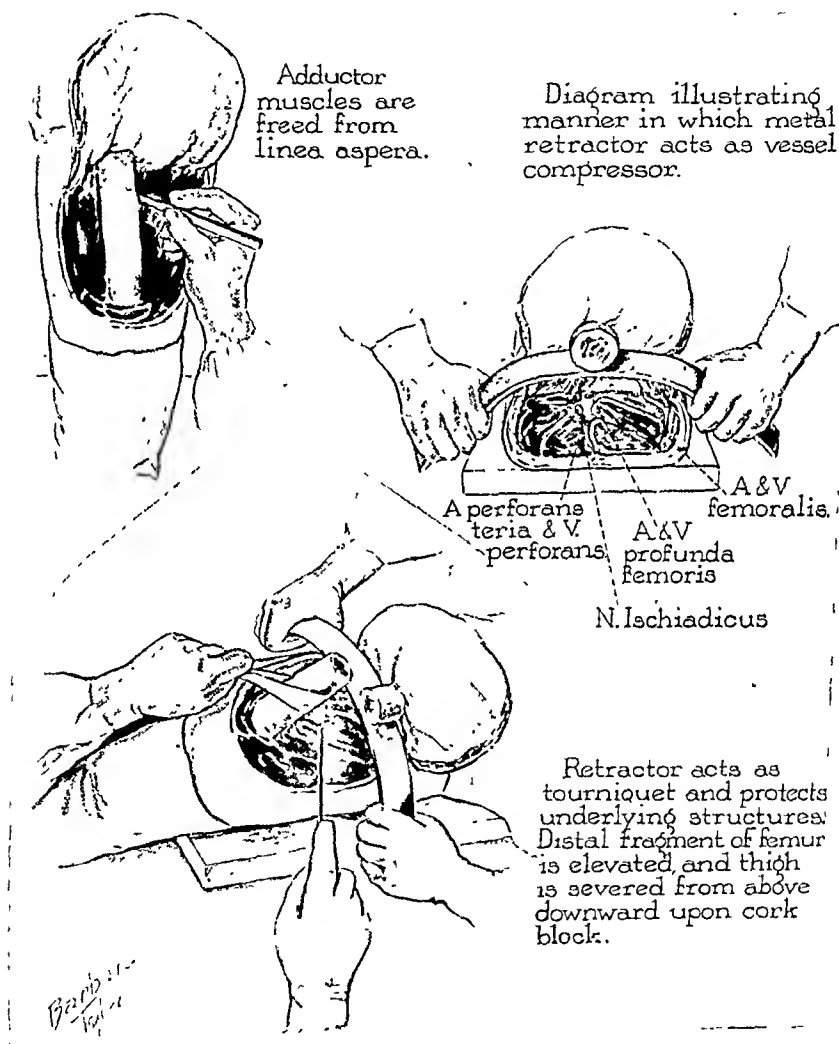


Fig. 1.

Three very fine interrupted sutures are sufficient to approximate muscle and fascia over the bone end. The skin is closed with interrupted sutures, and the stump is dressed with soft firm pressure. Drainage is not necessary.

The operation is frequently performed in the debilitated patient with impaired circulation. Therefore, the formation of dead spaces must be prevented, the blood supply of tissues whose vitality is already precarious must be preserved, and devitalization of tissues carefully avoided. To accomplish these ends, no tissues are to be promiscuously grasped in forceps. Sharp dissection, not with scissors, must be used throughout. The skin must never be dissected away from the underlying tissues. To preserve the blood supply of the flaps, the vessels should be ligated close to the distal edges of the flaps and not deep in the wound. Vessel ends beyond the ligatures should be only long enough to insure against slipping, to avoid leaving sclerosed tissue remnants in the wound. The very finest caliber of ligature and suture material is to be used throughout. All sutures should be tied without undue pressure and with only sufficient tension to approximate tissues.

It is assumed, of course, that every operative patient receives the proper preoperative and postoperative care. However, as in every surgical undertaking, and perhaps particularly in this field, attention to minute technical details and sound surgical principles will be rewarded with good results.

# PERFORATED LEIOMYOMA OF MECKEL'S DIVERTICULUM

## REPORT OF CASE

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THE tumors of Meckel's diverticulum are rare. Because of their rarity, we wish to report a case and briefly summarize the existing reports. Nygaard and Walters<sup>1</sup> have classified the neoplastic diseases of Meckel's diverticulum into carcinoma and sarcoma, as well as myoma, lipoma, neuroma, papilloma, and carcinoid tumors. A large variety of tumors are possible as in no other structure of the body are heterotropic tissues as common. Schaetz<sup>2</sup> found that in 43 per cent of thirty carefully examined diverticula, mucosa or tissue of other than ileac origin was present.

The tumors of Meckel's diverticulum do not form a large share of the pathology of this structure. In Greenblatt, Pund, and Chaney's<sup>3</sup> series of eighteen cases, only one tumor was found. In 50,000 pathologic specimens at the Johns Hopkins Hospital, Copeland<sup>4</sup> found only one tumor of Meckel's diverticulum. More common are the sequelae of the heteroplastic gastric and pancreatic tissue as inflammation and ulceration with hemorrhage and perforation. Intussusception and Littre's hernia, which Harkins<sup>5</sup> reports in conjunction with Meckel's diverticulum, are less frequent than inflammation but more common than tumor. Simons<sup>6</sup> suggests that myomas having their origin in the subserous tissue may be the origin of pulsion diverticula. This would even cast doubt upon the few reported cases; that is, they may really not have their origin in Meckel's diverticulum, but rather the diverticulum in which they are found may be secondary to the tumor. It is impossible to prove or to disprove such a contention, as there is no histologic landmark to identify Meckel's diverticulum, unless the omphalomesenteric communication with the umbilical structure is complete. Meckel's diverticulum is usually found in the terminal 100 cm. of the ileum, but according to Nygaard and Walters, may occur at any point in the gastrointestinal tract, from the cardia to the rectum, so that the reverse of Simon's hypothesis may also be true; that those cases of pulsion diverticula which he describes are actually abnormally placed Meckel's diverticula.

Myomas of the small intestine are comparatively rare. Raiford<sup>7</sup> believes that tumors of the small intestine rank in order of frequency: carcinomas, adenomas and sarcomas; lipomas and tumors of chronic in-

inflammatory origin; and finally the most uncommon, fibromas, myomas, carcinoids, hemangiomas, cysts, and endotheliomas. There may also be some doubt as to the benign nature of the myomas, as suggested by Klopp and Crawford.<sup>8</sup> They believe that one should not rely upon the microscopic diagnosis in determining whether or not a given leiomyoma is malignant or benign. In one of their series a recurrence was found thirteen years after resection. Strauss<sup>9</sup> has also reported a case which was microscopically benign, but which recurred after several months. It is, therefore, probable that the entire group of tumors should be considered under the heading of leiomyosarcoma. Nygaard and Walters<sup>10</sup> have been able to find the reports of twelve cases of sarcoma of Meckel's diverticulum and have added three of their own.



Fig. 1—Showing the Meckel's diverticulum extending from the ileum with the tumor closing at its apex.

Perforation of these tumors appear to be fairly common. In four of the cases reviewed by Nygaard and Walters, there were symptoms of diffuse or localized peritonitis. The three patients with diffuse peritonitis died, while the one patient with localized peritonitis was diagnosed as having a ruptured appendix and recovered.

The symptomatology of the tumors of Meckel's diverticulum is so confusing that diagnosis is rarely possible. The complaint is usually of abdominal pain in the lower abdomen with projection to the epigastrium. A palpatory finding of an abdominal tumor may be of consequence. In one case the tumor gave rise to an intussusception (Gray and Kernohan<sup>11</sup>). Gastrointestinal hemorrhage has been reported.

## CASE REPORT

F. K., a white male, 47 years of age, was referred to Cook County Hospital as a transfer from another hospital in Chicago from which he had been discharged for economic reasons. He stated that he had been ill for about six months, complaining of recurrent attacks of pain in the right side of his abdomen and in the periumbilical area. He found some relief from this pain by exerting pressure in the lower abdomen or striking this area with a hard object. Following such a bout of pain, eight weeks before admission, he suddenly had a very severe exacerbation. This was accompanied by a chill, fever, and vomiting. He was seen by a physician who made a diagnosis of acute appendicitis and advised an operation. He was admitted



Fig. 2.—Low-power photomicrograph demonstrating the tumor in the submucosa of the diverticulum.

to a hospital and prepared for a celiotomy. His physician reported to us that he made a right rectus incision. On opening the peritoneum he encountered a large abscess cavity which seemed to contain intestinal contents. He, therefore, drained the area and closed the abdomen. Following this intervention, the patient had a very stormy convalescence and a fistula formed which appeared to drain material from the small intestine.

The physical examination on admission to the Cook County Hospital revealed a very emaciated individual of about 40 years of age. The sclera were very pale. The heart and lungs were essentially normal. The abdominal wall was grossly eroded, the skin being denuded over an area of about ten inches in diameter. In the center



of this area there was a huge fossa, surrounding a small 6 mm. fistula from which material resembling "tobacco juice" constantly poured. Beneath this area there did not appear to be any tumor mass. Rectal examination did not reveal any tumor. The patient was given a small amount of methylene blue, which was recovered from the fistula in about two hours.

A suction motor was installed and a small catheter placed at the orifice of the fistula to remove constantly the discharge, and the denuded surfaces were covered with a paste of aluminum paint powder. Under this regime the denuded area rapidly healed. Cevitamic acid and vitamin K were administered parenterally. As the fistula closed symptoms of bowel obstruction developed. A diagnosis of regional enteritis with fistula and obstruction was made, and after two weeks of preparation an exploration was advised.

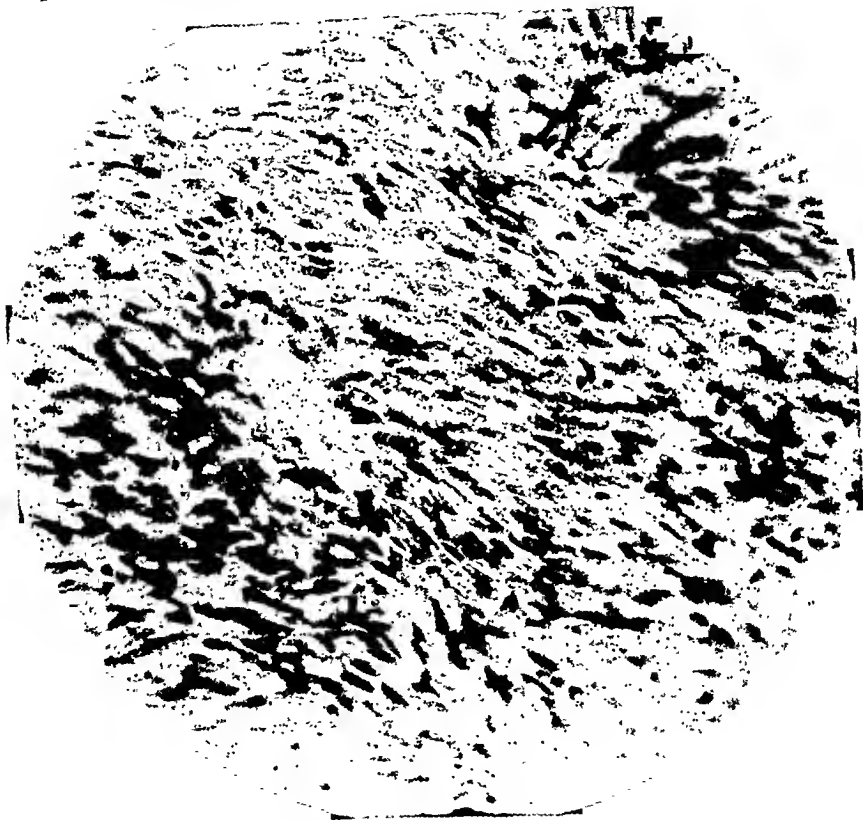


Fig 3.—High-power photomicrograph showing the interlacing bundles of smooth muscle cells.

The operation was performed under general anesthesia. Upon opening the abdomen it was found that the fistula led into a large abscess cavity. After a great deal of arduous dissection, the feeding point of the fistulous tract was found to be a perforated tumor at the apex of a diverticulum which was about 10 cm. long. The diverticulum was on the antimesenteric border of the ileum about 60 cm. from the ileocecal valve. The diameter of the diverticulum was about the same as that of the ileum. The diverticulum and the ileum at its base were resected for a distance of about 10 cm. in each direction. A side to side anastomosis was made and the abdomen closed with drainage.

The postoperative course was uneventful and the patient was discharged from the hospital on the twentieth postoperative day. When last seen, four months following the intervention, he appeared to be in excellent health.

**Pathology**—The specimen consisted in a piece of small intestine about 15 cm in length from the side of which, on the antimesenteric border, a pouch extended. This pouch had about the same diameter as the bowel and was about 5 cm long. The entire end of the pouch was involved in a tumor mass 10 by 15 by 10 cm, ragged and surrounded by much granulation tissue. The lumen of the bowel and of the pouch were continuous and appeared like normal bowel mucosa. The cut surface of the tumor mass was rubbery and solid. There was a 5 mm perforation through the side of this tumor connecting the lumen of the pouch with the outer surface of the tumor.



Fig 4—The open small intestine and the communication with the lumen of the diverticulum and tumor

**Microscopic**—The section of tumor mass removed from Meckel's diverticulum revealed interlacing bundles of fibrous connective tissue and muscle tissue cells. Under high power examination the nuclei of the muscle bundles appeared to be of a slightly oval to elongated shape with an ample amount of cytoplasm immediately adjacent to the nuclei. The fibrous stroma had a more spindle shaped appearance. Here and there between the bundles of muscle tissue were small focal accumulations of lymphocytes.

This tumor extended to the submucosa but was sharply demarcated from the submucosa. In one area the mucosa was ulcerated and the base of the ulcer was formed by vascular granulation tissue heavily infiltrated by round cells.

**Diagnosis.**—Active proliferating fibromyoma of Meckel's diverticulum

## SUMMARY

Tumors of Meckel's diverticulum are rare lesions, and myoma or myosarcoma is especially so. However, perforation of these tumors is not rare in comparison with their occurrence. A case of a perforated leiomyoma of Meckel's diverticulum with recovery is reported. It is suggested, however, that the microscopic diagnosis of the benign nature of this lesion is not certain; therefore, the prognosis for cure is to be guarded.

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# FIVE TUMORS OF THE ROUND LIGAMENT OF THE UTERUS— ONE A CAPILLARY HEMANGIOMA

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THE occurrence of tumors of the round ligament of the uterus is not a recent observation. Probably the earliest reference dates back to the time of Virchow.<sup>10</sup> He states that the yellowish mass which Walter removed (1805) from the right round ligament of a 37-year-old female was probably a myoma. It was many years later that Wells<sup>11</sup> reported 2 cases of fibrous tumors of the round ligament. One was the size of a large orange in a 40-year-old woman; the other was the size of a coconut in a woman, aged 50 years. Sänger<sup>8</sup> published the first review of round ligament tumors in 1883. He found 11 cases reported in the literature and added 1 of his own. His case was a fibrosarcoma in a 22-year-old female. This was the first sarcoma of the round ligament reported. Cullen<sup>3</sup> reported the first case of adenomyoma of the round ligament before the Johns Hopkins Medical Society in 1895. Subsequent cases have been reported with increasing frequency. In 1903 Emanuel<sup>5</sup> collected 76 cases of tumor of the round ligament and added 4 of his own. Taussig<sup>9</sup> (1914) reviewed the literature briefly and found 61 more cases, including his case of a spindle-cell sarcoma. Thus, up to that time 141 cases had been reported in the literature. Taussig found a statement regarding the pathologic nature of the tumors in 135 of the 141 cases. Of the 135 tumors, 79 were fibromyomas, 19 cysts, 1 a dermoid cyst, 30 adenomyomas, and 6 sarcomas.

In a brief review of the literature we have found 53 additional cases since the report of Taussig in 1914. There were 21 fibromyomas, 3 cysts, 14 endometriomas, 4 adenomyomas, 2 lipomas, 2 sarcomas, 2 cystadenocarcinomas, 1 benign aberrant ovarian tissue tumor, and 1 case of lithiasis of the round ligament.

We have 5 new cases to report, 1 endometrioma, 1 fibromyoma, 2 cysts, and 1 capillary hemangioma of the round ligament of the uterus. The capillary hemangioma is the first case of its kind to be reported in the literature.

## CASE REPORTS

CASE 1.—A married woman, aged 37 years, was admitted to the University of Kansas Hospitals complaining of a tender swelling in the right groin. The nodule was first observed following a blow to the pelvis in that region about five years before. She stated that the mass was more tender during menstruation.

In the right inguinal region directly at the site of the external inguinal ring there was a nodular tumor 2.5 by 3 cm. in size. It was very firm and tender. It appeared

to be attached to the right pubic bone. There was no evidence of hernia. X-ray examination showed no evidence of the palpated tumor nor was there any other pathology of the pelvis.

At operation the tumor was found attached to the terminal end of the round ligament and also to the pubic bone by fibrous tissue. It was excised with a portion of the round ligament.

The pathologic specimen consisted of an ovoid piece of tissue measuring 4.7 by 4 by 2.4 cm. The outer surface was rough, nodular in some portions, and several dark areas of hemorrhage were present. The tissue cut with resistance and presented a fibrous grayish white central portion. A few cysts at the periphery were filled with a dark brown semisolid material. Microscopic examination (Fig. 1) showed numerous endometrial glands surrounded by loose fibrous tissue, embedded in a dense fibromuscular stroma. Areas of degeneration, hyalinization, and monocytic infiltration were present.

The diagnosis was endometrioma of the round ligament of the uterus.



FIG. 1.—Section of tumor found in Case 1. Typical endometrial glands in cellular stroma ( $\times 135$ ).

CASE 2.—This 36-year-old colored female was admitted for removal of a fibromyoma of the uterus. A hard, round mass about 8 cm. in diameter was felt in the midline of the abdomen. It extended to 1 cm. below the umbilicus.

A supravaginal hysterectomy and left salpingectomy was done. At the same time the right round ligament, which contained a hard nodule 4 by 4.5 cm. in diameter at its terminal end, was also excised.

The uterus contained numerous subserous and mural fibromyomas and a polyp. The excised portion of the right round ligament was 7 cm. long, and attached to the outer end was a hard, circumscribed tumor nodule 1.5 cm. in diameter (Fig. 2).

The histologic picture of the round ligament and of the fibromyomas was similar and characteristic. Typical interlacing bundles of smooth muscle fibers were embedded in a hyaline fibrous tissue matrix (Fig. 3).

The diagnosis was fibromyoma of the right round ligament, multiple fibromyomas of the uterus, and endometrial polyp.

CASE 3.—This patient was a 40-year-old white housewife who was admitted with a complaint of hernia and goiter. She had noted a small mass in her left groin for

ten years and up until one year before admission it had been easily reducible. During the last year the mass had gradually increased in size. It had never been tender or caused any pain. Four days prior to admission she noted some pain and tenderness in the left groin, but there was no redness or other sign of inflammation. She had never had any vomiting.

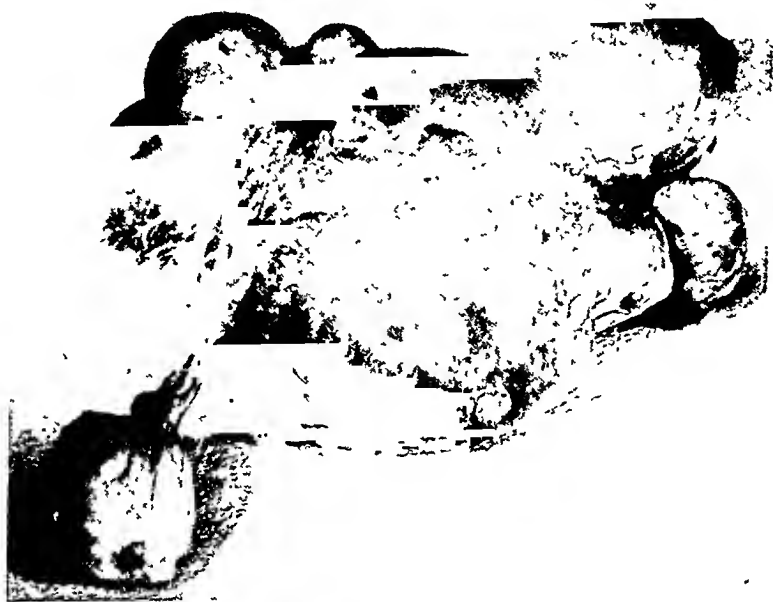


Fig. 2.—Fibroid uterus and fibromyoma of the end of the round ligament found in Case 2.



Fig. 3.—Section of tumor found in Case 2. Typical interlacing bundles of smooth fibers in fibrous tissue matrix ( $\times 135$ )

Examination of the left inguinal region revealed a mass 2.5 cm. in diameter, located in the upper left labium. The mass was fairly firm in consistency, freely movable, and slightly tender. It showed no evidence of acute inflammation. The external inguinal ring was relaxed, but the mass was irreducible.

A left inguinal herniorrhaphy was done. A cystic mass with a portion of the attached outer end of the round ligament was excised.

The pathologic specimen from the inguinal region consisted of a cystlike structure 2 cm. in diameter and 11 cm. long. It was attached to the round ligament. The

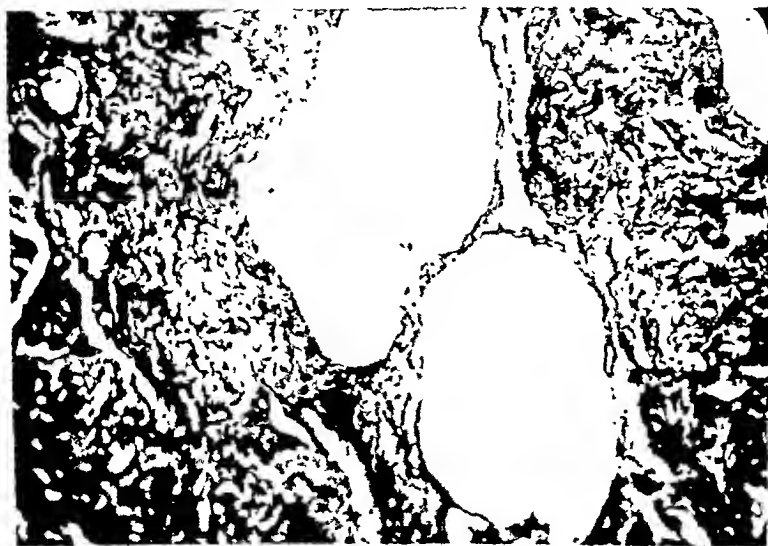


Fig. 1.—Section of tumor from Case 3, showing two small cysts in a loose hyaline fibrous tissue containing many small blood vessels (low power).



Fig. 5.—Section of cyst wall from Case 3, showing cavity lined by cuboidal and flattened epithelium (medium power).

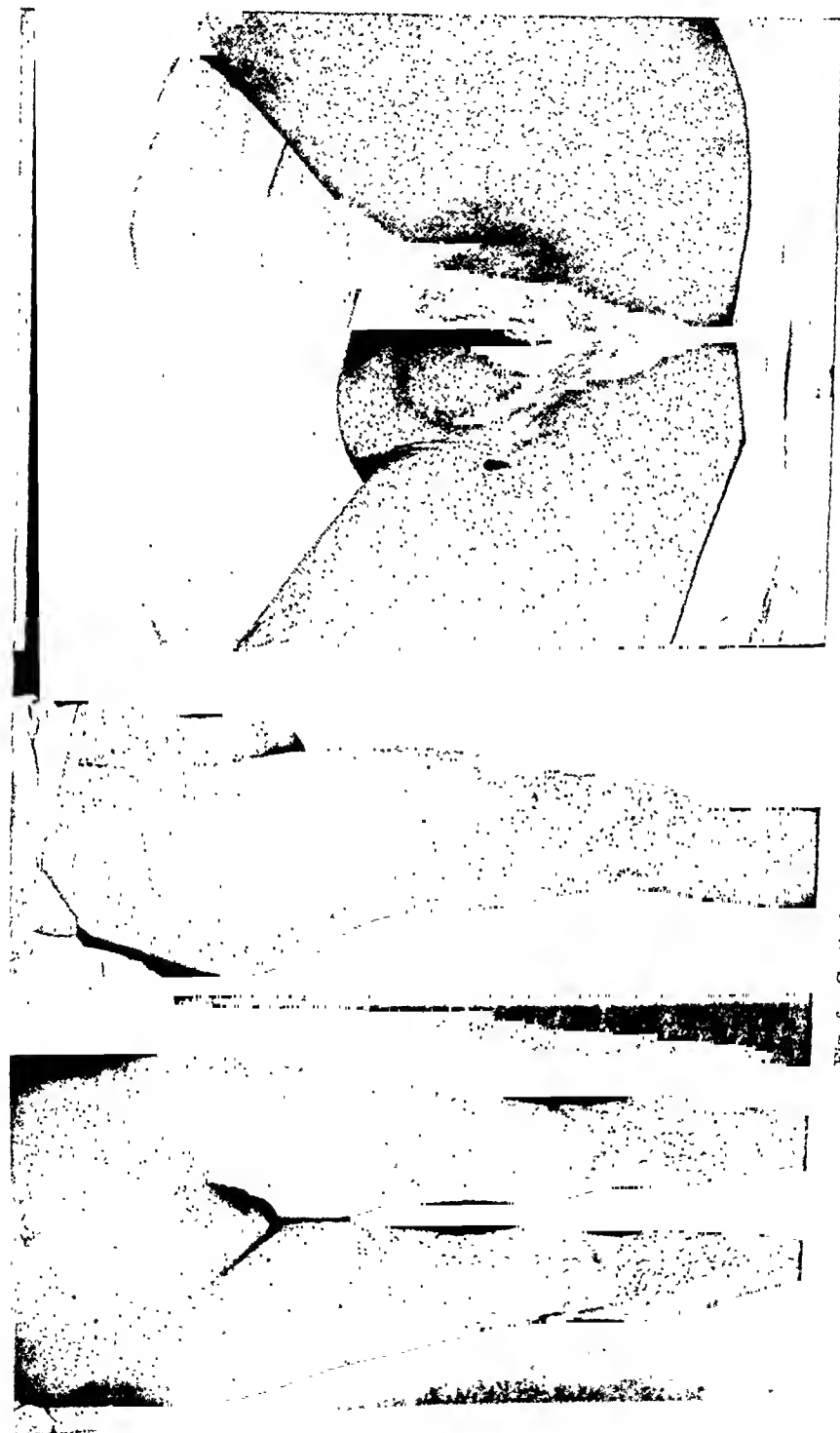


Fig. 6.—Cystic hygroma of the round ligament of the uterus (Case 4).



outer surface was roughened by fibrous tags and fatty tissue. Sectioning showed it to be thin walled and multilocular with each portion connected to the other. The cysts varied from 1 mm. to 1.5 cm. in diameter. They were filled with a clear mucoid material. Histologic section showed numerous cysts of varying sizes lined by cuboidal and, in some places, flattened epithelium (Figs. 4 and 5). The cyst wall was composed of loosely packed bundles of hyaline fibrous tissue intermingled with a few strands of smooth muscle fibers and blood vessels.

The diagnosis was congenital cyst of the round ligament and indirect inguinal hernia.

CASE 4.—This 38-year-old white female entered the hospital complaining of rupture, dysmenorrhea, and constipation. The hernia had been present for the past eight years. It was about the size of her thumb for the first four years and then began to enlarge. It had given her trouble for the past year and occasionally it would get hard but not very tender. The hernia reduced itself when she would lie down until the last four months, when it became irreducible.

Her general physical condition was good. In the right inguinal region there was a symmetrical mass about 5 by 8 cm. in size which extended into the right labium (Fig. 6). Pelvic and rectal examinations were negative.

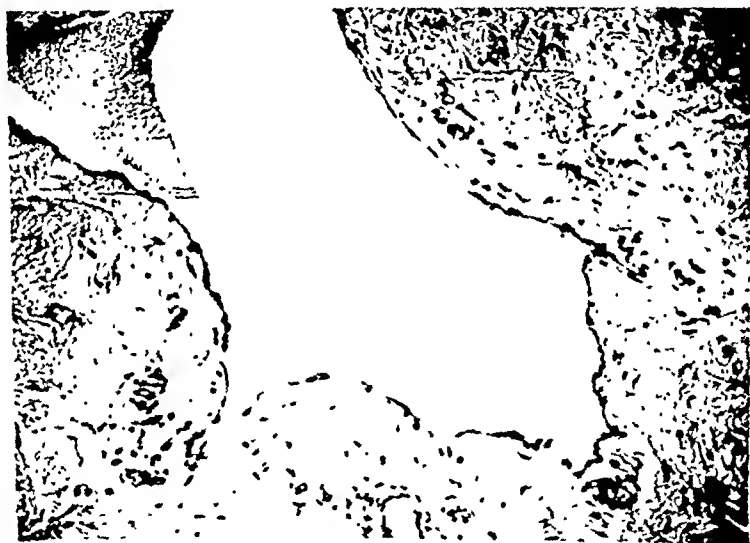


Fig. 7.—Section from Case 4, showing lining epithelium, loose stroma, and blood vessels of cyst wall (medium power).

At operation a cystic mass was dissected out of the right labium and inguinal canal. About 2 cm. above the external ring a hernial sac was found. The round ligament lay in the hernial sac and was attached to the cyst. The cyst, sac, and a portion of the round ligament were excised and a hernioplasty done.

The specimen consisted of an irregularly ovoid cyst which measured 11.5 by 6.5 by 3 cm. and weighed 115 Gm. The thin wall of the cyst was translucent and somewhat lobulated. It contained a thin fluid. Two centimeters of the round ligament were attached at one end. Histologic section showed a number of cystic, cleftlike spaces which were lined by a layer of swollen cuboidal epithelial cells. The larger cysts were all lined by the same type of epithelium and divided by fine trabeculae. The walls were composed of hyaline fibrous tissue containing irregular bundles of smooth muscle cells and numerous blood vessels (Fig. 7).

The diagnosis was cystic hygroma of the round ligament.

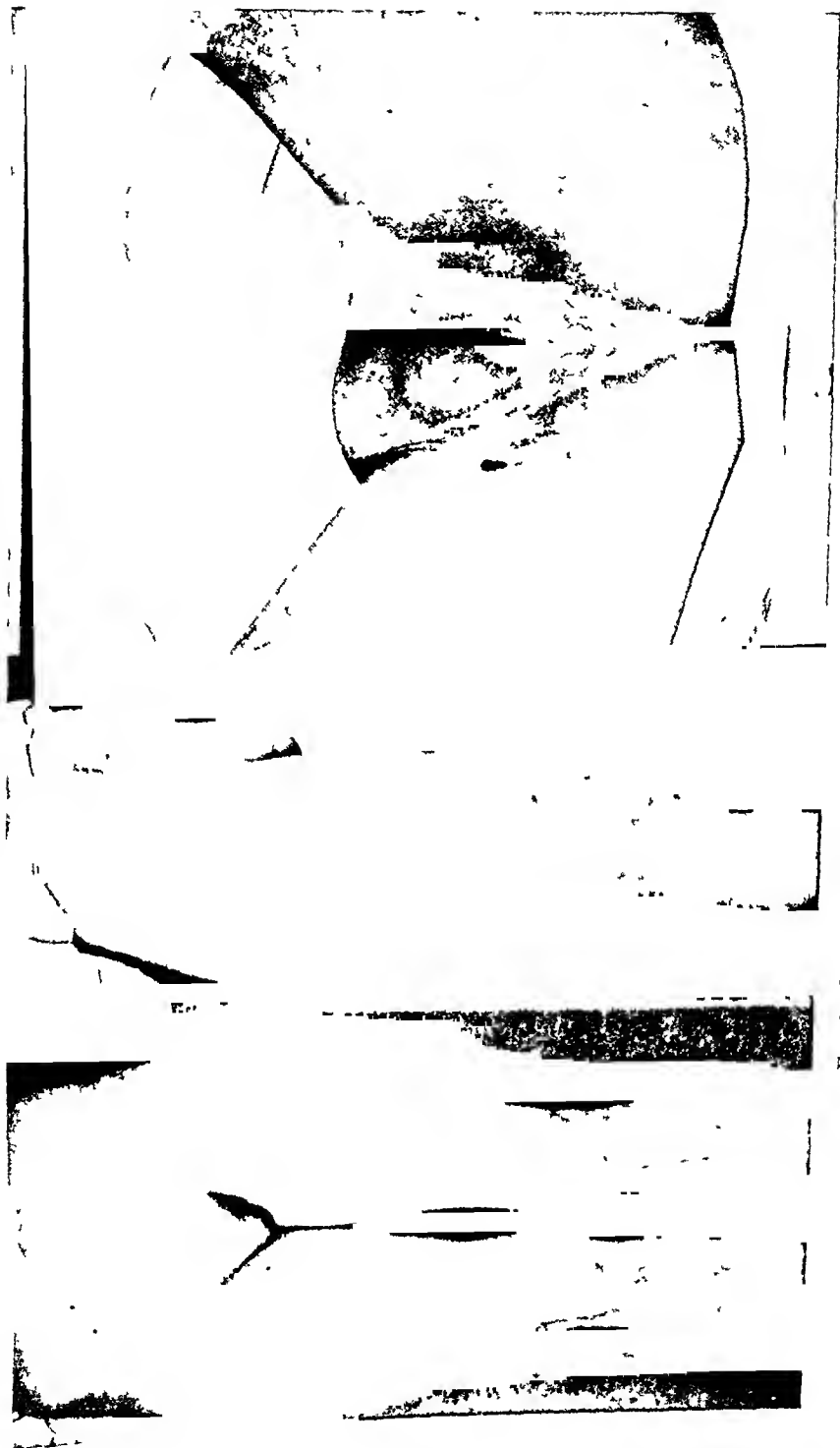


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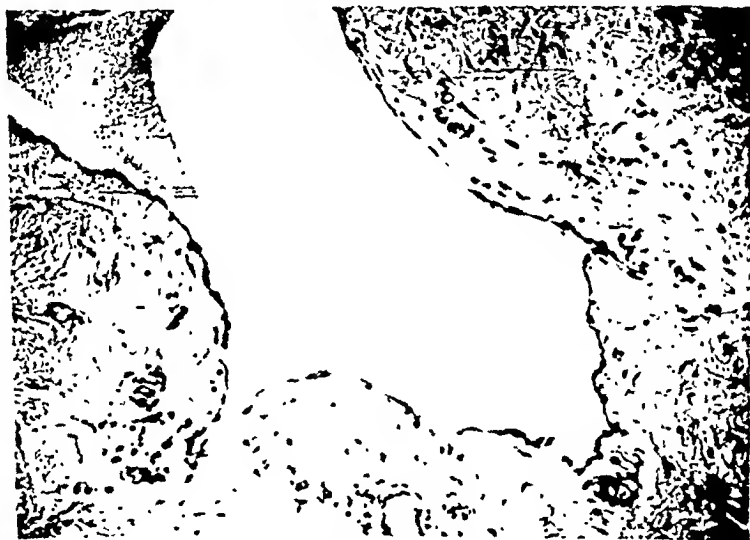


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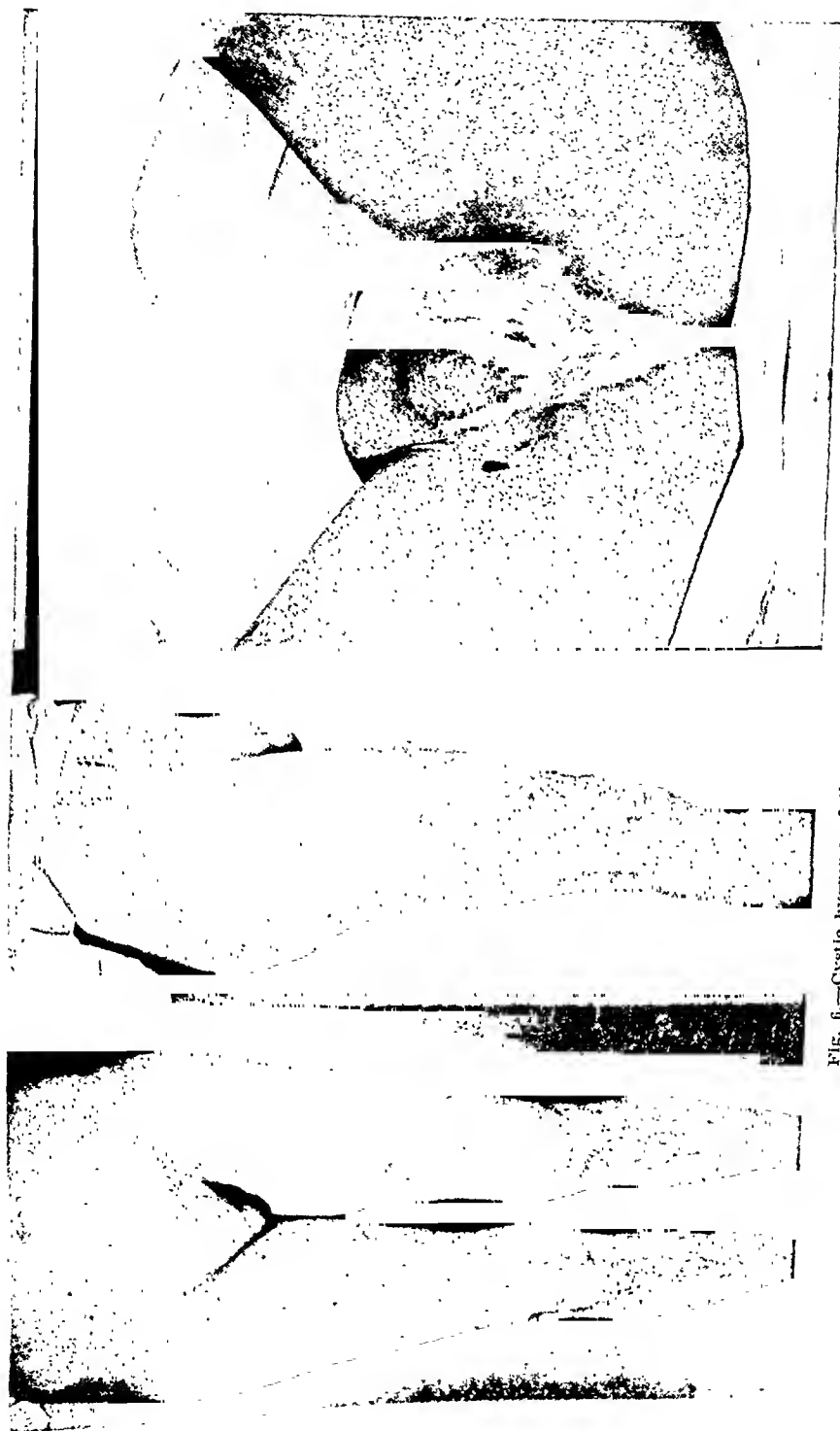


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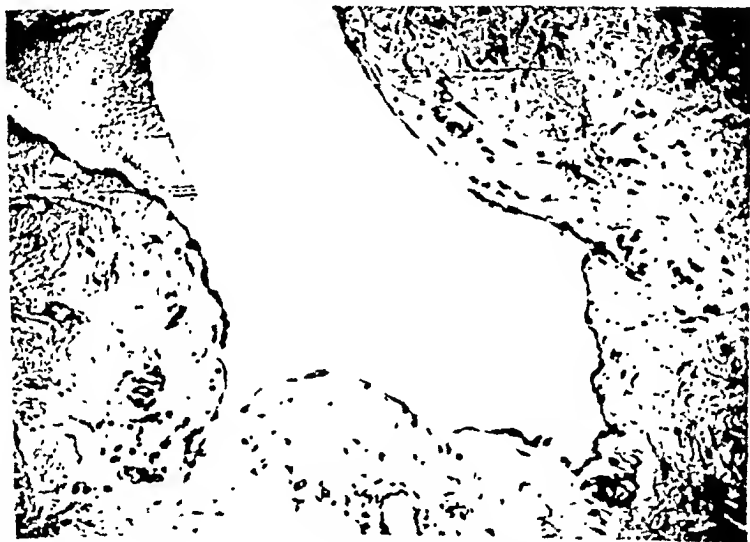


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The diagnosis was cystic hygroma of the round ligament.

CASE 5.—This patient's chief complaint was rupture. She was a 34-year-old white housewife. She first noticed a small mass in her right inguinal region about one and one-half years ago when she was on her feet for any length of time. Lately the mass had progressively increased in size. She complained only of a feeling of pressure and occasional nausea if she pressed on the mass. She thought that it disappeared when she lay flat on her back.

A mass about 3 cm. in diameter was palpated in the right inguinal region. It was more noticeable when the patient was standing. It was moderately soft in consistency and bulged more when she coughed or strained. It was not reducible. The clinical impression was that the patient had a right inguinal hernia with possibly some incarcerated omentum in the hernial sac.

At operation a large mass was found in the right inguinal region. It was very vascular and bled readily. It was somewhat hourglass-shaped and extended into the abdomen with a constriction at the internal ring. After removal it measured 10 by 4.5 by 4 cm. (Fig. 8). A hernioplasty was then performed.



Fig. 8.—Capillary hemangioma of the round ligament of the uterus found in Case 5; it measured 10 by 4 by 4 cm.

The specimen was an irregularly shaped and lobulated structure. It was fairly well encapsulated and the capsule showed numerous fibrous tags and some hemorrhage. The cut section in one area showed numerous tiny cystic structures containing a watery hemorrhagic fluid. The cut section through other areas of the mass appeared to be light gray and cellular. The histologic section presented an angiomatous structure in which there were numerous small and large endothelial lined cleftlike spaces (Fig. 9). This was supported by a fibromuscular stroma. In some fields fairly large blood vessels were present. There was also some round-cell infiltration and a few areas of hemorrhage. The endothelial cells here and there showed some swelling but otherwise presented nothing unusual. The cells making up the trabeculae and supporting the sinusoids were oval, rounded, or spindle-

shaped. Their cytoplasm was of a fibrillar nature with indistinct cell outlines. The nuclei tended to be vesicular, but a few of them were hyperchromatic. No mitotic figures were seen. Other sections stained with Masson's stain showed some of the stroma cells to be stained blue. This was suggestive of angioendothelioma in some areas, but, if so, it was not malignant. The final diagnosis was capillary hemangioma of the round ligament.

#### DISCUSSION

Although tumors of the round ligament of the uterus are relatively infrequent, they should be kept in mind in considering any inguinal mass in the female. Our five cases demonstrate four different types of tumor involvement of the round ligament. The history given by the patient with endometrioma of the round ligament was diagnostic. She



Fig. 2.—Section from tumor in Case 5, showing extreme vascularity. The capillaries and endothelial-lined sinuses are separated by round- and spindle-shaped stroma cells (X135).

was a woman in the childbearing age with a mass in her right inguinal region. This had been present for five years and was characterized by its becoming more tender during her menstrual period. Beek<sup>1</sup> emphasizes that similar symptoms may be produced by herniation of an ovary into the canal of Nuck.

Our two cases of cyst of the round ligament are interesting because they demonstrate the size they may attain. Transillumination of the tumor in Case 3 gave a clue to the diagnosis. Both of these cases had an associated indirect inguinal hernia. Neel<sup>2</sup> emphasizes the high incidence of inguinal hernia and inguinal endometriosis and adenomyomas as reported by Cullen,<sup>4</sup> Sampson,<sup>5</sup> Christopher,<sup>2</sup> and others.

We were not able to find any report in the literature of a case of capillary hemangioma of the round ligament of the uterus. The tumor

in our patient was extremely vascular and bled readily during the operation. Histologic section showed some areas which were suggestive of angioendothelioma. The Masson stain showed that in these areas some of the stroma cells stained brown like the endothelial lining of the capillaries and sinuses and hence were of the same origin. The connective tissue elements were stained blue. No mitotic figures were seen. Dr. H. R. Wahl, pathologist at the University of Kansas, did not believe the tumor to be malignant even though some of the areas were suggestive of angioendothelioma.

Neel<sup>b</sup> recently reviewed the prevailing theories about the pathogenesis of endometrium-like tumors of the round ligament. This was done so thoroughly that it is not necessary to present them again.

#### SUMMARY

1. Tumors of the round ligament of the uterus are uncommon but not rare. Over 200 cases are reported in the literature. They should be considered, therefore, in the diagnosis of masses in the inguinal region of the female.

2. Our 2 cases of cyst of the round ligament also had an indirect inguinal hernia.

3. We have had 5 cases of tumor of the round ligament in the past seven years. They were an endometrioma, a fibromyoma, a congenital multilocular cyst, a cystic hygroma, and a capillary hemangioma with areas suggestive of benign angioendothelioma.

4. The first case of capillary hemangioma of the round ligament of the uterus is reported.

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## HEMANGIOMA OF THE LARGE BOWEL\*

VERNE C. HUNT, M.D., LOS ANGELES, CALIF.

IN 1923 Alfred J. Brown reviewed 20 cases of hemangioma of the intestinal tract. Nineteen of those had been recorded in the literature previously and to them he added an instance of such a lesion in the jejunum. In 1930 McClure and Ellis added to Brown's original series 1 case of their own and 4 from the literature. Since 1931, Baneroff (9 cases), Raiford (3 cases), Rankin and Newell (1 case), Barga and Dixon (3 cases), Weber (1 case), Ackerman (3 cases), Merchant (2 cases), and Sawyer (1 case) have reported surgical and autopsy findings of hemangiomas of the intestinal tract, making a total of approximately 48 cases of such vascular tumors of the intestine recorded in the literature. In 3 of these the entire intestinal tract was involved by multiple hemangiomas; the small intestine, including the duodenum, was the site of one or more of these tumors in 27 cases; the intraperitoneal colon in 6 cases; the rectum and sigmoid in 2 cases; the rectum in 8 cases; and in 2 instances the location of the lesion was not stated.

To date there are apparently only 20 cases recorded in which hemangiomas have been encountered in the large bowel surgically or at necropsy. It is my good fortune to have seen one of these cases, that of an hemangioma of the cecum and appendix, encountered in the course of a cholecystectomy for gallstones which I performed on April 22, 1926, while a member of the surgical staff of the Mayo Clinic. Quoting from the surgical notes pertaining to the lesion of the cecum and appendix the record states: "The lateral and anterior surfaces of the cecum and the appendix were involved in a very extensive process which has the appearance of an angioma. The vessels were tortuous and beaded and involved the lower three inches of the cecum and the entire appendix." (Fig. 1.) The appendix was removed. Buie and Swan reported this case in 1929, and Barga and Dixon and Rankin, Barga, and Buie have included it among 5 cases of hemangioma of the colon and rectum, and the case was likewise included in Baneroff's series of cases in 1931.

In the recorded cases of hemangioma of the intestine the lesions have varied in size and extent from capillary nevi to huge cavernous hemangiomas circumferential in their involvement of the intestine. The infrequency with which extensive cavernous hemangioma has been encountered in the large bowel seems to justify reporting an instance of such a lesion occupying the rectosigmoid and the entire rectum with extension to the uterus, successfully operated upon by a two-stage abdominoperineal resection of the sigmoid and rectum and hysterectomy.

\*Presented before the Fifteenth Annual Meeting of the Western Surgical Association, Topeka, Kan., Dec. 6 and 7, 1919.

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## CASE REPORT

The patient, a female, 39 years of age, was seen July 29, 1940. In brief, rectal bleeding had occurred intermittently since birth and most consistently with a movement of the bowels. During the patient's entire life there had been but few intervals of three weeks' duration when no bleeding occurred. Bright red blood had been passed many times on arising in the morning and at other times independent of a bowel movement. There had been a number of massive hemorrhages from the rectum and on several occasions transfusion of blood was necessary. The menstrual periods had always been regular and normal and no relationship between menstrual periods and rectal bleeding had ever existed. There never had been significant



Fig. 1.—Hemangioma of the cecum and appendix.

rectal pain. At 18 years of age the patient's hemoglobin was 30 per cent, and there after the hemoglobin ranged from 30 to 50 per cent. During the past twenty-four years various forms of local treatment had been instituted for what was considered an obscure rectal lesion. Hemorrhoidectomy had been performed at 14 years of age and again at 18 years of age, and injection and searing of rectal mucosa on several occasions resulted in questionable temporary benefit. Roentgenologic examination had been essentially negative. Her physician stated in a letter: "The patient has this odd hemorrhagic condition in the lower colon and rectum which looks like an hemangioma."

Upon examination the patient appeared to be very anemic, but was fairly well nourished. The systolic blood pressure was 140, and the diastolic pressure was 90. There was a rough systolic cardiac murmur, but otherwise the general physical examination was essentially negative with the exception of the suggestion of a mass in the lower left quadrant of the abdomen. There was considerable scarring of the anal and rectal mucosa which was somewhat thickened, and there were a



FIG. 2. Hemangioma involving the rectosigmoid and posterior surface of the uterus.

number of shotty nodules high in the rectal mucosa. A review of recent roentgenologic films of the rectosigmoid presented some evidence of thickening of the walls of the rectum and rectosigmoid.

The patient was admitted to St. Vincent's Hospital, where further investigation failed to cast additional light on the nature of the lesion from which bleeding was

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cision as a permanent colostomy, and placing the distal inverted end into the lower angle of the midline incision. A transfusion of 600 c.c. of blood was given immediately following the operation.

Three weeks later, on Aug. 22, 1940, the entire sigmoid and rectum were removed through the combined abdominoperineal procedure (Figs. 4, 5, and 6). The blood loss attending the perineal part of the procedure was considerable, for the hemangiomatous process extended laterally into perirectal structures. The operation



FIG. 4. Hemangiomatous process in rectum and rectosigmoid (external view of the resected specimen).

occurring. Urinalysis showed a specific gravity of 1.019 and was normal with the exception of a few red blood cells and an occasional leucocyte. The concentration of the hemoglobin was 5.2 Gm. per 100 c.c. of blood (31 per cent); the erythrocytes numbered 2,610,000 and the leucocytes 2,400 with approximately a normal differential count. So much thorough investigation had been engaged in previously that surgical exploration was advised on a preoperative diagnosis of a tumor of the rectosigmoid. A transfusion of 600 c.c. of blood elevated the hemoglobin to 7.5 Gm. per 100 c.c. of blood and the erythrocytes to 2,970,000.

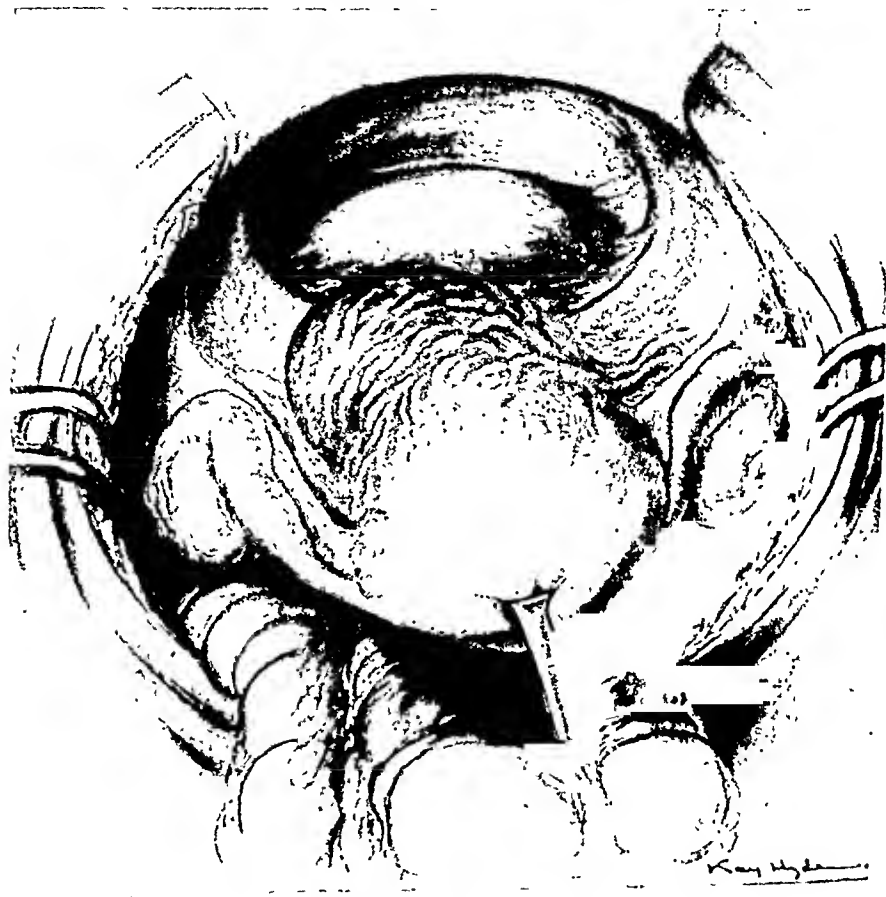


Fig. 3.—Extension of the hemangiomatous process onto the anterior surface of the uterus.

At operation, July 31, 1940, through a low median line incision, there was disclosed an extensive hemangioma involving the anterior wall of the rectosigmoid for a distance of about 12 cm. above the peritoneal reflexion and apparently extending well down to involve the major part of the rectum (Figs. 2 and 3). The distal half of the uterus on both the anterior and posterior walls was extensively involved in the hemangiomatous process. Examination of the remainder of the colon and the small intestine failed to disclose any other lesion. After due consideration it seemed that only through a combined abdominoperineal resection of the sigmoid and rectum could the best prospects of cure be offered. A subtotal hysterectomy was performed and the first stage of a two-stage abdominoperineal resection was accomplished by dividing the sigmoid and bringing the proximal end through a left split muscle in-

The patient was dismissed from the hospital on Sept. 15, or the twenty-fourth day following the abdominoperineal resection, and returned to her home one month later with the perineal wound practically closed and her general condition good.

In a letter dated Nov. 18, 1940, three months following the resection, the patient reported that the hemoglobin had recently been found to be 75 per cent; also, that the colostomy, much to her surprise, was no great source of trouble but of much less annoyance and embarrassment than the bleeding from the rectum had been for so many years.



FIG. 6.—Mucosal surface of the resected specimen

was followed immediately by a transfusion of 600 c.c. of blood. Even though bleeding was accurately controlled at the time of operation, the drainage from the perineal wound contained considerable blood for some days. On the sixth postoperative day the concentration of hemoglobin was 6.5 Gm. per 100 c.c. of blood (39 per cent) and the erythrocytes numbered 2,227,000. A transfusion of 600 c.c. of blood was given at this time, following which the convalescence was an entirely orderly one.



Fig. 5.—Hemangiomatous process in rectum and rectosigmoid (mucosal surface of the resected specimen).



small or large intestine, and repeated and oftentimes exsanguinating hemorrhage has characterized lesions situated in the rectum. In a number of instances rectal bleeding occurred in early childhood. Mechanical intestinal obstruction and intussusception have characterized the clinical manifestations in a number of the lesions of the small intestine. Merchant recently reporting two cases of intussusception due to an hemangioma of the small intestine cited three other instances in which this complication had occurred. Even though intussusception occurred in nearly one-fifth of the cases of hemangioma of the small intestine, this complication occurred in no instances in which the lesion was situated in the colon. Mechanical obstruction occurred in two cases (Bue and Swan, and Sawyer) of extensive hemangioma of the intraperitoneal colon, and in each instance a filling defect in the colon was visualized roentgenologically. Bancroft has said: "In any patient who complains of persistent bleeding from the rectum over a period of years, usually beginning in infancy, hemangioma should be suspected. If the angioma occupies the rectum or rectosigmoid the diagnosis may be readily made from the appearance of the lesion as seen by proctoscopic examination. Unless the tumor is pedunculated roentgenologic examination is of little aid in the diagnosis."

#### TREATMENT

The mortality rate following treatment of hemangiomas of the large intestine has been approximately 50 per cent. Death in most instances has been due to continued or recurrent massive hemorrhage. Local cauterization of lesions in the rectum and rectosigmoid has been followed by few satisfactory results. Multiplicity of these tumors in the rectum and sigmoid has frequently defeated local methods of treatment. Tuffier reported a case in which death followed massive hemorrhage from two hemangiomas at the sigmoid following successful cauterization of a similar lesion in the rectum. Radical resection of the segment of the intraperitoneal colon harboring an hemangioma has seldom been instituted. However, Bue and Swan in 1929 and Sawyer in 1939 recorded two cases of extensive obstructive hemangioma of the colon which were successfully removed by the Mikulicz exteriorization procedure. The ingenious and successful method which Bancroft employed in the treatment of an extensive hemangioma of the sigmoid involving a segment of the colon corresponding to the distribution of the superior hemorrhoidal vein was apparently based on Ribbert's theory that growth of an hemangioma is by projecting solid buds of endothelium into adjacent tissues without invasion of or communication with surrounding vessels and therefore the vascular tumor has no anastomotic connection with other vessels. Bancroft's case was that of a 17-year old boy who had had rectal bleeding since he was 15 months of age, in whom the diagnosis of hemangioma was made by proctoscopic examination. In

The surgical specimen was described by Dr. James E. Kahler, Pathologist at St. Vincent's Hospital, as follows: "*Gross Description.—Uterus:* The specimen consists of the supravaginal portion of the uterus and the coned out portion of the cervix, together measuring 8.5 by 5 by 4 cm. On the anterior surface of the fundus, beginning 2.5 cm. above the peritoneal reflexion, there is a mass of engorged veins lying principally on the left. On the posterior surface of the fundus in the midline, there is a large mass of dilated veins raised 1 cm. above the surface. This mass fans out on both sides as well as upwards, extending to within 2.5 cm. of the top of the fundus. *Rectum and Sigmoid:* The specimen consists of 45 cm. of large bowel, including the anus, rectum and rectosigmoid. Beginning at the anus and extending proximally 30 cm. the bowel wall is involved by a cavernous hemangioma. At its upper extremity the lesion is sharply demarcated, but at the anus the tumor gradually fades out into numerous fine venules. The mucosa over the lesion is uneven because of the protrusion of varices, but is intact except for innumerable pin point ulcers. On cross section the hemangioma involves all of the coats of the bowel wall and extends into the surrounding adipose tissue. The lesion is more marked in the submucosa and serosa than in the mucosal or muscular layers.

"*Microscopic.—Uterus:* The serosal lesion is composed of thin-walled veins engorged with red cells. The muscle of the cervix and lower uterine segment contains an increased number of large dilated veins. The endocervix and endometrium are normal. *Rectum and Sigmoid:* The tumor is composed of thin-walled veins engorged with red cells. The submucosa is solid hemangioma. The serosa and muscularis are honeycombed by large groups of varices. In the mucosa nearly all of the varices lie just above the muscularis mucosa; few occur immediately below the surface epithelium. The mucous membrane is atrophied and the glands are widely separated. Over each solitary follicle there is a superficial ulceration."

*Diagnosis.*—1. Hemangioma of the pelvic peritoneum involving the serous coat of the distal half of the uterus. 2. Cavernous hemangioma of the rectum and rectosigmoid.

#### TYPES OF LESIONS

Brown, in 1923, grouped hemangiomas of the intestine into four classes as follows: (1) Multiple tumors on the vascular arcades which appear as small red nodules situated in the submucosa and connected with either the arteries or veins of that portion of the intestinal wall. Microscopically they are either nevi or cavernous angiomas. (2) The submucous tumor which grows toward the lumen of the intestine tends to ulcerate the overlying mucosa. (3) The submucosal tumor which may grow to such size that it either obstructs the intestine or causes a change in the normal peristalsis and brings about intussusception. (4) The diffuse ringlike lesion which, beginning in the submucosa, involves the muscularis and constricts the lumen of the intestine and brings about intestinal obstruction. It would seem that the case herein reported represents still another type of lesion, which may be described as a diffuse intramural lesion involving the entire thickness of the bowel wall and which, even though it was circumferential, was neither constrictive nor obstructive.

#### CLINICAL MANIFESTATIONS

Hemorrhage from the bowel has been the predominant symptom of hemangiomatous lesions whether the lesion has been situated in the

small or large intestine, and repeated and oftentimes exsanguinating hemorrhage has characterized lesions situated in the rectum. In a number of instances rectal bleeding occurred in early childhood. Mechanical intestinal obstruction and intussusception have characterized the clinical manifestations in a number of the lesions of the small intestine. Merchant recently reporting two cases of intussusception due to an hemangioma of the small intestine cited three other instances in which this complication had occurred. Even though intussusception occurred in nearly one-fifth of the cases of hemangioma of the small intestine, this complication occurred in no instances in which the lesion was situated in the colon. Mechanical obstruction occurred in two cases (Bue and Swan, and Sawyer) of extensive hemangioma of the intraperitoneal colon, and in each instance a filling defect in the colon was visualized roentgenologically. Bancroft has said: "In any patient who complains of persistent bleeding from the rectum over a period of years, usually beginning in infancy, hemangioma should be suspected. If the angioma occupies the rectum or rectosigmoid the diagnosis may be readily made from the appearance of the lesion as seen by proctoscopic examination. Unless the tumor is pedunculated roentgenologic examination is of little aid in the diagnosis."

#### TREATMENT

The mortality rate following treatment of hemangiomas of the large intestine has been approximately 50 per cent. Death in most instances has been due to continued or recurrent massive hemorrhage. Local cauterization of lesions in the rectum and rectosigmoid has been followed by few satisfactory results. Multiplicity of these tumors in the rectum and sigmoid has frequently defeated local methods of treatment. Tuffier reported a case in which death followed massive hemorrhage from two hemangiomas of the sigmoid following successful cauterization of a similar lesion in the rectum. Radical resection of the segment of the intraperitoneal colon harboring an hemangioma has seldom been instituted. However, Bue and Swan in 1929 and Sawyer in 1939 recorded two cases of extensive obstructive hemangioma of the colon which were successfully removed by the Mikulicz exteriorization procedure. The ingenious and successful method which Bancroft employed in the treatment of an extensive hemangioma of the sigmoid involving a segment of the colon corresponding to the distribution of the superior hemorrhoidal vein was apparently based on Ribbert's theory that growth of an hemangioma is by projecting solid buds of endothelium into adjacent tissues without invasion of or communication with surrounding vessels and therefore the vascular tumor has no anastomotic connection with other vessels. Bancroft's case was that of a 17-year old boy who had had rectal bleeding since he was 17 months of age, in whom the diagnosis of hemangioma was made by proctoscopic examination. In

brief, upon abdominal exploration the lesion appeared to be confined to the distribution of the superior hemorrhoidal vein. The vein was isolated from the artery and ligated, following which 10 c.c. of 40 per cent sodium salicylate was injected into the vein distal to the ligature. A temporary colostomy was made high in the sigmoid. This was closed nearly one year later and inasmuch as no bleeding from the rectum had occurred since the superior hemorrhoidal vein had been injected, the assumption that the patient was cured seems warranted.

There appears to be sufficient evidence at hand to indicate that extensive intramural hemangioma of the rectum and colon may usually be treated successfully only through radical extirpation of the involved segment of the bowel. An entirely satisfactory result was obtained in the case of extensive hemangioma of the rectum and rectosigmoid herein recorded, and removed by abdominoperineal resection.

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# Editorial

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## "Explosion Jitters"

THERE was a time when the surgeon was haunted by the fear of wound infection. The novice assistant, the careless nursing staff, or the unreliable catgut manufacturer were thought to harbor the ghost. Today the fear of explosion furnishes a more dramatic substitute. Whereas wound infection stole upon surgeon and patient insidiously, in the still small hours of the night, fire comes upon the operating room scene in the full glare of the "Klieg lights." It has even been known to announce its arrival with the fearful detonation of a bomb. There can be little doubt that the ghost of fire hides among the accoutrements of the anesthetist.

We are accustomed to the use of illuminating gas in our basements and kitchens and of gasoline in our automobiles. We rarely think of the danger involved, and yet the chemical nature of ether, ethylene, or cyclopropane does not create a greatly different hazard. Why should there be extreme apprehension in the operating room and little or none in the kitchen and garage? Three possible reasons may be suggested.

1. Oxygen is mixed with ignitable substances in the operating room and not at home: Apparatus may, therefore, contain or deliver ignitable mixtures.

2. Anesthetic apparatus is moved about, assembled or dismantled either in accommodating itself to the respiratory movements of the patient, or at the convenience of the operator: Hence static electricity of differing potentials may accumulate.

3. Electrically operated instruments or the actual cautery used in the operating room may, especially if defective, constitute a source of ignition.

An ignitable gas or liquid escaping from its container in the pure state must be mixed with adequate oxygen, and vaporized if a liquid, before it will take fire. Extremely dilute mixtures are, in many instances, violently explosive; whereas, higher concentrations may fail to explode or even to burn when exposed to spark or flame. Knowledge of the exact concentrations of a particular substance, which will ignite or explode when mixed with air or artificial atmospheres of higher oxygen tension is of no practical value since, in the process of making and dispersing any gaseous mixture, there may exist, at one time or another, all concentrations of any component. Unless oxygen is needed for physiologic reasons (those recognized as indications for oxygen therapy outside the operating room) anesthetic atmospheres containing the same tension of oxygen as atmospheric air or slightly higher are more suitable for the patient's welfare and are apt not to produce violently explosive mixtures with any agent.

Atmospheres contaminated by ignitable substances, and containing oxygen or nitrous oxide, should be kept in closed containers without leaks (anesthetic apparatus with carbon-dioxide absorption technique) during the period when electrical apparatus must be used in the vicinity. If open techniques of administration of ignitable anesthetic agents are used, or if leaking containers or pipe lines are suspected, the use of electric equipment had better be prohibited.

Electrostatic charges are prone to accumulate on surfaces subject to movement and friction. If contamination of the contained or surrounding atmosphere is suspected, it is important to bring into intimate contact, by handling, all the component parts of apparatus and these with patient and anesthetist before fresh contact or separation of the component units takes place.

The "housing and grounding" elements in moveable equipment may easily become defective. For this reason, electric equipment in hospitals should be frequently and intelligently inspected and kept in perfect repair.

The surgeon or hospital superintendent should insist upon intelligent supervision of anesthetic administration in his institution. No rules for "safe practice" can replace the minute-to-minute supervision of a responsible anesthetist in the operating room. A "jittery" attitude on the part of others only adds to the hazard.

The danger of explosion may be compared to that from hemorrhage. The operating room mortality rate from blood loss is far in excess of that from explosion. Yet the surgeon, the hospital superintendent, the public press, and the patient do not expect the mortality from hemorrhage to be reduced by sets of rules prepared by committees and posted in the operating room corridors. Deaths from hemorrhage are less frequent as knowledge of anatomy, physiology, and surgical technique is disseminated among surgeons. Likewise fires and explosions in operating rooms will become less frequent as knowledge of physics, chemistry, and technical skill is disseminated among anesthetists.

In the meantime it is well to remember that fire or explosion accidents which injure patients or operating room attendants are rare indeed. When such accidents occur, there would seem to be no more reason for hysterical outbursts in the press and for "jitters forever after" on the part of those concerned, than in the case of a death in the operating room from hemorrhage. By all means, increase our knowledge of the physical and chemical factors involved in the ignition of anesthetic agents. In the meantime let us put the responsibility where it belongs—on the anesthetist. Let us see that his knowledge and skill is the best obtainable, and if he has an accident, let us look upon it as we would upon any slip in technique or diagnosis by surgeon or consultant and stop the development of this new disease "explosion jitters."

—Rolph M. Waters, M.D.

Madison, Wis.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## CYSTIC DISEASE OF THE BREAST

### A CRITICAL REVIEW

HERBERT H. DAVIS, M.D., OMAHA, NEB.

IN 1825 Sir Astley Cooper described cystic disease of the breast: "The marks of distinction in this disease are: 1st, the health remaining perfect; 2dly, the almost entire absence of pain, unless there is a suppurative tendency in the cysts, when I have known the disease painful; 3dly, the swelling being firm, smooth, and not tender to the touch; 4thly, when a fluid forms, the fluctuation being very distinct, and a slight blue tinge being observable when it approaches the skin; 5thly, the fluid, when evacuated, having the transparency of water, with a very slight yellow tinge, and this is sometimes succeeded by a discharge of mucus." He also stated that when the cyst is excised it does not return. Since that time there have been many conflicting opinions about the etiology, pathology, and treatment.

Because of these differences of opinion, many names have been applied, commonest of which are hydatids of the breast by Cooper, 1825; serocystic tumor by Brodie, 1846; "*la maladie kystique des mamelles*" by Réclus, 1883; cystadenoma by Schimmelbusch, 1892; mastitis chronica cystica by König, 1893; abnormal involution by Warren, 1905; senile parenchymatous hypertrophy by Bloodgood, 1906; fibroadenomatosis cystica mammae by Semb, 1928; cystiferous desquamative epithelial hyperplasia by Cheate and Cutler, 1931; mastopathia by Whitehouse, 1934; and many others.

### PATHOLOGY

The main theories of pathology may be discussed under the following headings: (1) retention cysts; (2) chronic inflammation; (3) involutional process; (4) epithelial hyperplasia; (5) neoplastic process; (6) sweat gland origin.

1. *Retention Cysts*—Birkett (1850) considered the disease to be due to stenosis of the lactiferous ducts, resulting in failure to discharge the secretion.

The following two theories, i.e., the inflammatory and the degenerative, agree with this principle. They go a step further and discuss the causes of duct obstruction which leads to retention of secretions and consequent formation of cysts.

2. *Chronic Inflammation*.—In 1867, Virchow named the condition interstitial mastitis.

König (1893) is usually credited with formulating the theory of inflammation. He introduced the name "mastitis chronica cystica." He stated that the lesion often involved both breasts. Frequently swelling and pain preceded the menstrual periods; with the onset of the flow the tumor decreased in size but several small lumps of leatherlike hardness remained. He found the interstitial connective tissue highly infiltrated with leucocytes.

Delbet (1893) thought that the infection entered the mammary ducts at the nipple, producing a primary inflammation of the connective tissue. The same manner of infection was described by Roloff (1900), who thought that infected material could be pressed into the ducts of the nipple by the pressure of clothes.

Sasse (1897) classified two forms of cystic disease, one a chronic interstitial inflammation, as described by König, and the other a pure neoplastic epithelial growth. Of eleven cases reviewed, he considered five to be due to interstitial inflammation.

Schultze stated that Maly, Kausch and Borst, Tonpet and Glantenay, Betagh, Franco, Corvil and Petit, Conotein, Pilliet, Phocas, and Tillaux were in favor of the inflammatory origin.

It is rather generally agreed by pathologists that an interstitial round cell infiltration is common in cystic disease of the breast. The debated point is whether this inflammatory reaction is cause or effect. According to the above theory, the inflammation causes scar tissue formation which contracts about the lactiferous ducts, narrowing them to the point where secretion is retained. In blue-domed cysts the epithelium is often thin or lacking. On the other hand, round-cell infiltration is not always present, and some other origin is needed to explain these cases. The present consensus of opinion is that cystic disease of the breast is not a primary inflammatory process. The name "chronic cystic mastitis," therefore, is improper. The commonly found lymphocytic infiltration in this disease is thought to be a secondary change.

3. *Involutional Process*.—In 1880, Billroth found cysts of the breast common in older women at the time of involution in the breast. In the vicinity of the cysts were usually cystic dilatations of small ducts, in the interior of which papillary excrescences often arose. The large cysts had little or no epithelium. The cysts usually arose in hypertrophied breast tissue. He believed that formation of cysts was as follows: During involution the connective tissue of the breast contracted, the epithelium of the acini shrank and disappeared, and the epithelium remained a little longer in the ducts. An unequal contraction of connective tissue compressed some ducts and pushed others apart. In the latter an exudation resulted which was mixed with destroyed epithelial cells and some blood.



In 1906 Bloodgood used the term "senile parenchymatous hypertrophy." He spoke of two types of disease, the cystic and the adenocystic, the latter corresponding to that described by Schimmelbusch. He believed that the adenocystic type was caused by parenchymatous hypertrophy, in which the dilated ducts and acini were filled with proliferating epithelial cells. He compared cystic disease of the breast to prostatic hypertrophy.

Warren in 1905 termed the condition "abnormal involution." Von Saar in 1907 showed that after involution there remained some young functioning cells which reacted to ovarian impulse. Cystic disease not only occurred at the climacteric but also at the involution of each menstrual cycle. Berka in 1912 and Bertels in 1913 found changes in each involutional stage which could be the beginning of chronic mastitis. Syms (1916) showed that following lactation a defective process of involution commonly leaves "residual lactation acini." In 1917, McFarland attributed the formation of all cysts to presenile or senile involution. Schultz (1933) reported an 18-year-old girl whose breasts developed cystic disease during three months of amenorrhea.

It is generally known that the common age of this disease is between 40 and 50 years, which is the period of breast involution.

4. *Epithelial Hyperplasia*.—Cheatle and Cutler (1931) considered that the cystipherous process was biologically and morphologically distinct from an epithelial neoplasia or tumor formation. The desquamated cells were dead and, therefore, incapable of multiplication. They also stated that it was not an atrophic process, but one of pathologic activity, and, therefore, not a process of involution.

5. *Neoplastic Process*.—The first comprehensive histologic description of cystic disease of the breast was made by Brissaud (1884), who examined the pathologic specimens removed by Réclus. Finding that the cysts were usually in the periphery, he believed that they arose in the acini rather than in the ducts. He gave the lesion the name "*d'épithéliome kystique intra-acineux*."

Schimmelbusch in 1892 considered the disease to be neoplastic and named it "cystadenoma." He described the multiplicity of smaller cysts in the outer portion of the breast which made the lobules sharply circumscribed and showed a definite ridge. The feeling of small tumors in the breast was like that of a "bag of balls." He stated that the primary change was an increase in the number of acini in the lobule, much like the proliferation in a lactating breast; then the epithelium became several layers thick and finally filled the acini, after which the epithelium in the center degenerated. There was never any leucocytic infiltration or sign of inflammation.

Six of the eleven typical cases described by Sasse (1897) were thought to be of a neoplastic nature. These, usually multiple cysts, were frequently bilateral and easily became carcinoma.

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TABLE I

AUTHOR	YEAR	CASES	CARCINOMA	PER CENT
Schimmelbusch	1892	43	3	7.0
Sasse	1897	9	2	22.0
Roloff	1900	11	4	36.3
Greenough and Hartwell	1903	30	3	10.0
J. C. Warren	1905	115	15	13.0
Theile	1909	19	3	15.8
Speese	1910	35	9	25.7
Semb	1928	100	24	24.0
Kazhevnikoff	1930	80	6	7.5
		442	69	15.6

cause of chronic cystic mastitis is not known. There is no evidence that it is precancerous. In every instance in which I have exposed a blue dome, the tumor has been a benign cyst." This latter statement has led to great debate, and now it is rather generally agreed that carcinoma very rarely arises in the epithelium of a blue-domed cyst.

2 *Evidence of Cystic Disease in Breasts Removed for Carcinoma*—Several investigators, in studying the specimens of breasts removed for cancer, have also made microscopic sections in distant parts of the breast. Table II will show the number of cases in which an accompanying cystic disease was found.

TABLE II

AUTHOR	YEAR	CARCINOMA	CYSTIC DISEASE	PER CENT
J. C. Warren	1905	507	15	3.0
Deaver and McFarland	1917	335	23	6.5
Fischer	1925	151	21	14.0
Semb	1928	140	112	80.0
McGlannon	1930	100	8	8.0
Morpurgo	1930	196	47	24.0
Lewis and Geschickter	1938	2,675	29	1.1
		4,104	255	6.2

Semb (1928) stated that 80 per cent of mammary cancer was secondary to fibroadenomatosis. Junge (1932) found cystic disease associated with mammary carcinoma in 83 per cent of his cases. Cheate and Cutler (1931) stated that 20 per cent of cancer arose from cystiferous desquamative epithelial hyperplasia. On the other hand, Lewis and Geschickter (1938) concluded: "These figures would seem to indicate that cystic disease and adenosis are not precancerous lesions, and that radical operations should not be performed as frequently as they are." They admitted, however, that "approximately 30 per cent of comedo or duct carcinoma showed histologically a relationship to adenosis (Schimmelbusch's disease)."

My experience is that, if in cases of carcinoma of the breast the supposedly normal parts are studied, a high proportion will show associated cystic disease, with all stages of epithelial hyperplasia. I should like

The question of where the epithelium or connective tissue plays the leading role in cyst formation was discussed at the "19. Congress Deutschen Gesellschaft für Chirurgie" in 1890, where Schimmelbush spoke of the neoplastic nature, and König in conjunction with Virchow spoke of the inflammatory origin. Haeckel and Tietze considered it neoplastic.

Opposed to the theory of the neoplastic origin of cysts is the diffuseness of the involvement.

6. *Sweat Gland Origin.*—Occasionally the cysts are lined by pale cells, which von Saar spoke of as "*blasse Epithelien.*" Because of this pale epithelium resembling that of sweat glands, Krompecher in 1909 stated these cysts were derived from sweat glands. He named the disease "hidrokystoma mammae."

In my opinion, since the breast is often considered to be a modified sweat gland, the presence of pale epithelium would rather be expected; but this fact does not explain the formation of all cysts, many of which do not have this pale epithelium. This theory does not help solve the problem of treatment of this disease.

At present cystic disease of the breast is considered not to be a primary inflammatory process. The term "chronic cystic mastitis" is, therefore, incorrect. Lymphocytic infiltration in this disease, generally agreed to be common, is considered a secondary change. Whether the process begins in the connective tissue or is a primary epithelial hyperplasia is still debated. Probably there are two forms of the disease, a cystic type, in which the cysts are due to retention, and an adenocystic type, in which multiple small cysts are due to epithelial hyperplasia.

A study of endocrine relationship to the breast will aid in solving this problem.

#### THE RELATION OF CYSTIC DISEASE TO CARCINOMA OF THE BREAST

The earliest writers upon the subject of chronic cystic mastitis, among them Sir Astley Cooper (1825), recognized the occasional association with carcinoma. Schimmelbush (1892) found carcinoma in 3 of 43 cases he collected from the literature. This subject is considered here under the following headings: (1) evidence of unsuspected carcinoma in breast tissue removed for cystic disease, (2) evidence of cystic disease in breasts removed for carcinoma; (3) determination of the number of cases of cystic disease in which carcinoma later develops.

1. *Evidence of Unsuspected Carcinoma in Breast Tissue Removed for Cystic Disease.*—The figures in Table I suggest that carcinoma develops much more frequently in breasts with cystic disease than in normal breasts.

In 1906 Bloodgood regarded the adenocystic form as precancerous in 10 per cent of cases. In 1921 he changed his opinion and states: "The

(1931) believed that "painful breasts" were due to overstimulation by the corpus luteum hormone. He reported relief in 80 per cent of his cases by oral administration of ovarian residue. Estrin is commonly given for cystic disease. Whitehouse (1934) stated that the logical treatment should be inhibition of the hypophysis. On the other hand, administration of gonadotropic substance is frequently advised.

Some clinical facts contrasting fibroadenoma and cystic disease of the breast give valuable clues in regard to etiology. Fibroadenoma occurs most commonly in women between 20 and 30 years of age, not before puberty or after the menopause, and enlarges rapidly during pregnancy. Cystic disease arises later, usually between 35 and 50 years of age, occurs occasionally during the first few years after the menopause, and disappears during pregnancy.

A brief review of the endocrine control of the breast may be of interest. The main organs controlling the breast are the ovaries and the anterior lobe of the pituitary. The estrogenic hormone stimulates growth of the lactiferous ducts and of the nipples, sensitizes the duct endings for the action of progesterin, and inhibits the anterior pituitary. Estrin is secreted by the granulosa cells of the Graafian follicle, by the corpus luteum, and by the placenta. It increases during the intermenstrual cycle, reaching its peak just before the menstrual period, when it suddenly decreases. During pregnancy its concentration in the blood increases until the expulsion of the placenta, when it disappears.

Progesterin, secreted by the corpus luteum, stimulates the development of the acini of the breast. During corpus luteum development in the latter part of the intermenstrual cycle, this hormone is increased in the blood. Corpus luteum continues to form progesterin during the first half of pregnancy. There is, unfortunately, no good quantitative test for progesterin.

The anterior pituitary is necessary for development of the breast. The sex hormones are thought to act through the anterior pituitary to produce breast growth. The breasts atrophy in hypophysectomized animals, even in those given large doses of sex hormones. The ovarian hormones inhibit the anterior pituitary. As ovarian function decreases near the time of the menopause, this inhibition is lessened, resulting in excess amounts of gonadotropic hormones. It is at this period of life that chronic cystic mastitis is most likely to occur.

In this age group the ovarian action decreases, and clinical improvement or cures may result by treatment with estrogenic substances. Most of these breasts show epithelial hyperplasia indicating marked stimulation of the epithelium. It is unphysiologic to expect lack of hormone to cause stimulation. Some hormone must be stimulating these terminal ducts. The gonadotrophic hormones are in abundance at the age this disease is common. It is known that the pituitary is necessary for breast growth. Is it therefore not logical that the gonadotropic

to suggest that, in the study of mammary carcinoma, sections from the supposedly normal breast tissue be studied routinely as well as those made from the tumor itself.

The case history of a patient with mammary carcinoma rarely reveals an antecedent benign lump. Of 444 cases of carcinoma, Johnson (1925) obtained the history of preceding cystic disease in only 2. Campbell (1934) found such in the history of only 4 of 88 cancer cases.

3. *Determination of the Number of Cases of Cystic Disease in Which Carcinoma Later Develops.*—A clinical investigation to determine the risk of carcinoma developing later in cases of chronic cystic mastitis may aid in solving the problem. Some information upon this subject is given in Table II made up from a study of the literature.

TABLE III

AUTHOR	YEAR	CASES	CARCINOMA	PER CENT
Greenough and Simmons	1914	83	4	4.8
Bloodgood	1921	123	3	2.3
Peck and White	1922	63	0	0.0
Johnson	1925	107	2	1.9
Campbell	1934	232	1	0.4
Klingenstein	1935	54	2	3.7
Lewis and Geschickter	1938	250	1	0.4
S. Warren	1940	340	14	4.1
		1,258	27	2.1

In the cases presented in Table III there was no treatment at all or merely local excision of the cyst or cystic area. Mathews (1936) stated that in twenty years he had aspirated "fully 50 cysts" and only 1 had become cancerous. Adair, in discussing Mathews' paper, stated that carcinoma occurred after operation in blue-domed cysts in less than 2 per cent of cases. These statistics indicate that danger of carcinomatous development in cystic disease is much less than microscopic studies of tissue removed would indicate.

There is rather general agreement that carcinoma does not commonly arise in the thin epithelium of large blue-domed cysts. These are the cysts which can be palpated and are commonly excised. Small cysts with proliferating epithelium may not be palpable and are, therefore, not so often excised by the surgeon. Most authorities agree that this type is much more dangerous, especially before the menopause. Because of the microscopic changes frequently seen, showing all stages of proliferation of epithelium from benign cyst to comedo carcinoma with invasion of the stroma, and because of the frequent finding of unsuspected adenocystic disease in other parts of breasts removed for carcinoma, I believe this lesion causes carcinoma much more frequently than is usually thought.

#### ENDOCRINE CONTROL OF THE BREAST

Many conflicting reports have been made upon endocrine causes of mammary disease and upon treatment by hormone therapy. Cutler

of the blue-domed variety, lined by thin epithelium; and the adenocystic type, with many small cysts, lined by hyperplastic epithelium which gives the impression of marked activity.

Carcinoma very rarely develops in the epithelium of a blue-domed cyst. On the other hand, there may be risk of carcinoma arising in the adenocystic type.

Endocrine imbalance is probably the cause. A theory is presented in which overactivity of the anterior pituitary, associated with deficient inhibition by the ovaries, is considered responsible for cystic disease of the breast.

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hormones of the pituitary, with lessened inhibition from the ovaries, cause this stimulation? I wish to propose the above as a theory of the etiology of cystic disease of the breast. I realize this is unproved, but it seems to be logical. Bloodgood stated that cystic disease of the breast does not occur in obese women, a fact which also fits this theory. In aged women well beyond the menopause, when the gonadotropic hormones are decreased, cystic disease does not occur.

#### TREATMENT

The most common treatment of cystic disease of the breast is simple excision of a single cyst or resection of a small cystic area. This local resection for a diffuse lesion of one or both breasts seems rather illogical. Aspiration of a single blue-domed cyst has been recommended for treatment as well as for diagnosis. This procedure has the same objection, because small cystic areas always exist in the remaining breast tissue. After local excision or aspiration, new cysts arise later in 15 to 20 per cent of cases. Most of these arise in the same breast but may occur in either. As would be expected, more recurrences arise in the adenocystic type than in a breast with large single cysts. The surgeon, knowing that cancer is a definite risk, constantly fears its development in the remaining breast tissue.

Because of the frequent recurrences of cysts and the danger of cancer, Cheate and others have advised bilateral simple mastectomy for the adenocystic type. This seems radical, as follow-up reports show that cancer develops in only 2 per cent of cases not operated upon or treated with local excision. Most women would prefer two or three operations consisting of simple excision to losing one or both breasts. As the lesion is diffuse, removal of one breast is no assurance that carcinoma will not occur in the other breast. Bilateral simple mastectomy is certainly the best safeguard for the future but is rather radical.

In spite of the above objections, simple excision usually is advised in the cystic type and a little more extensive local excision or even removal of one or both breasts in the adenocystic type.

In the future we should strive to combat the cause. This means an attack upon the endocrine imbalance which probably causes the lesion. Many advise injections of estrin. If the theory I have presented is correct, roentgen-ray therapy to the pituitary should be used. Estrin would also be indicated, as it would help to correct the imbalance between ovary and pituitary and also to inhibit the pituitary.

Surgery should be reserved for biopsy to rule out carcinoma and for failure of endocrine therapy.

#### CONCLUSIONS

For practical purposes cystic disease of the breast may be considered to be of two types: the cystic type, with one or more fairly large cysts



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# Review of Recent Meetings

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## THE TWENTY-FOURTH ANNUAL MEETING OF THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

PAUL HOLINGER, M.D., CHICAGO, ILL.

THE TWENTY-FOURTH Annual Meeting of the American Broncho Esophagological Association was held June 3, 1941, at the Mid Day Club, Cleveland, Ohio, President Gabriel Tucker, Philadelphia, presiding.

The President's Address consisted of a discussion of **Chemotherapy of the Lung Administered by the Endobronchial Route**. Tucker discussed Kolmer's work on bronchial disinfection by vaccines, bacteriophages, and antiviruses. He then presented experimental data regarding the endobronchial insufflation of the sulfanilamide group of drugs, stressing particularly the use of sulfanilamide and sulfadiazine. Dogs were used to determine the local reaction of the bronchial mucosa to these drugs as well as to determine the blood level of these drugs following intrabronchial insufflation. The dosage was 0.5 Gm. per kilogram body weight and this quantity was insufflated into the lung every second day. The left bronchus was inoculated in each case, the right bronchus serving as a control. After ten days the tracheobronchial tree and lungs were examined. No difference was noted in the mucous membranes on the two sides of the tracheobronchial tree in which this dosage was adhered to and no obstruction was found in any case. No local reaction was found histologically. The blood level showed a marked increase proportional in each case to the dose which had been administered. However, the rate of absorption from the lung was not considered important since the control of this level could be maintained successfully by administration through the intraoral route. In one instance a large dose of sulfadiazine, twice the normal dose, was administered intrabronchially, and while no actual bronchial obstruction was noted macroscopically, there was some evidence of atelectasis in the area beyond the point of insufflation. It was felt that this was entirely due to an error in the dosage administered. Sulfanilamide was more rapidly absorbed from the bronchus than was sulfadiazine, but this factor was felt to be an undesirable one since the attempt is made by this type of therapy to increase the concentration of the drug and maintain it at a high level in the bronchus itself. Tucker's conclusions were that the sulfanilamide drugs were well tolerated by the lung and by the bronchi without irritation and that bronchial obstruction was not caused when a normal dosage was used.

In the **Presentation of Instruments**, C. L. Jackson, Philadelphia, presented a new tracheotomy tube which had a simplified shield and gate to hold the inner tube in place.

**Carlos E. Pitkin, Cleveland. Repeated Severe Hemoptysis Necessitating Pulmonectomy.**—Pitkin presented the case report of a patient 31 years of age who had had repeated massive hemoptyses. While the apparent source was the left bronchus, the actual site of the hemoptysis could at no time be determined bronchoscopically. Pneumothorax and other measures were unsuccessful in controlling

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THE TWENTY-FOURTH Annual Meeting of the American Broncho Esophagological Association was held June 3, 1941, at the Mid Day Club, Cleveland, Ohio, President Gabriel Tucker, Philadelphia, presiding.

The President's Address consisted of a discussion of Chemotherapy of the Lung Administered by the Endobronchial Route. Tucker discussed Kolmer's work on bronchial disinfection by vaccines, bacteriophages, and antiviruses. He then presented experimental data regarding the endobronchial insufflation of the sulfanilamide group of drugs, stressing particularly the use of sulfanilamide and sulfadiazine. Dogs were used to determine the local reaction of the bronchial mucosa to these drugs as well as to determine the blood level of these drugs following intrabronchial insufflation. The dosage was 0.5 Gm. per kilogram body weight and this quantity was insufflated into the lung every second day. The left bronchus was inoculated in each case, the right bronchus serving as a control. After ten days the tracheobronchial tree and lungs were examined. No difference was noted in the mucous membranes of the two sides of the tracheobronchial tree in which this dosage was adhered to and no obstruction was found in any case. No local reaction was found histologically. The blood level showed a marked increase proportional in each case to the dose which had been administered. However, the rate of absorption from the lung was not considered important since the control of this level could be maintained successfully by administration through the intraoral route. In one instance a large dose of sulfadiazine, twice the normal dose, was administered intrabronchially, and while no actual bronchial obstruction was noted macroscopically, there was some evidence of atelectasis in the area beyond the point of insufflation. It was felt that this was entirely due to an error in the dosage administered. Sulfanilamide was more rapidly absorbed from the bronchus than was sulfadiazine, but this factor was felt to be an undesirable one since the attempt is made by this type of therapy to increase the concentration of the drug and maintain it at a high level in the bronchus itself. Tucker's conclusions were that the sulfanilamide drugs were well tolerated by the lung and by the bronchi without irritation and that bronchial obstruction was not caused when a normal dosage was used.

In the Presentation of Instruments, C. L. Jackson, Philadelphia, presented a new tracheotomy tube which had a simplified shield and gate to hold the inner tube in place.

Carlos E. Pitkin, Cleveland: Repeated Severe Hemoptysis Necessitating Pulmonectomy.—Pitkin presented the case report of a patient 31 years of age who had had repeated massive hemoptyses. While the apparent source was the left bronchus, the actual site of the hemoptysis could at no time be determined bronchoscopically. Pneumothorax and other measures were unsuccessful in controlling

the hemorrhages. A pneumonectomy was performed and careful dissection of the lung failed to reveal the source of bleeding. The patient, however, has had no further hemoptysis. The vessels and bronchi were normal, but a slight fusiform dilatation was found in the left lower lobe. In the discussion of the paper, **Porter Vinson**, Richmond, Va., suggested that such hemorrhages, without x-ray or physical findings, were almost always due to slight fusiform bronchiectasis. He suggested the insufflation of sulfanilamide to control bleeding during the hemoptysis, and the use of an aspirating tube to remove granulation tissue which may be a source of the hemorrhage. **Richard Overholt**, Boston, felt that such massive hemorrhages could be due only to erosion of bronchial vessels or to a calcified gland, and could not originate in the peripheral vessels. **Gabriel Tucker**, Philadelphia, suggested the use of tannic acid and gallic acid in controlling this type of hemorrhage, applied to the mucous membranes directly.

**Albert H. Andrews, Jr.**, Chicago. **The Functional Examination of Respiration in Obstructive Diseases.**—A clinical method of examination was described which records the movements of air in and out of the chest. The apparatus consisted of a Benedict Roth metabolism apparatus modified essentially by the addition of a high speed recording drum for demonstrating the qualitative characteristics of respiration.

Respiratory obstruction in the larynx and trachea showed a symmetrical slowing of inspiration and expiration at the extremes of the vital capacity tests. Bronchial asthma was characterized by a curved expiratory tracing and obstructive emphysema by a moderately slowed velocity and trapping of air on successive maximum expiratory movements.

The examination was of therapeutic usefulness inasmuch as short periods of therapeutic trial could be made under controlled and measured conditions, thereby permitting the selection of therapeutic procedures which had been demonstrated to be effective. The effects of oxygen, helium, positive pressure, and epinephrin by inhalation, were presented. The course of the disease could be followed and the continued effectiveness of the therapeutic procedure could be demonstrated. The examination was of value in the study of obstructive diseases because it made possible the mathematic expression and recording of the characteristics of respiration. The correlation between the results of the functional respiratory examination and the bronchoscopic findings was considered by Andrews as of value in clarifying the knowledge of the nature of the obstructive diseases.

An outline of the diagnosis of bronchial asthma was presented which endeavored to cover the various related factors and to show the role of the functional examination of respiration.

**Arthur E. Hammond**, Detroit. **Perforation of the Trachea by a Mediastinal Tumor (Hodgkin's Disease).**—Hammond presented a report of a 15 year old boy who had had clinical and roentgenologic findings of a mediastinal tumor which was producing compression stenosis of the trachea. Intrabronchial invasion was found on bronchoscopic examination and the material removed for histologic examination established the diagnosis of Hodgkin's disease invading the trachea and right bronchus. The value of the laminographic study of the trachea was beautifully illustrated by roentgen films which demonstrated the obstruction. In the discussion **William Hudson**, Detroit, reported three cases of tracheal obstruction produced by aortic aneurysms and one case of a thyroid adenoma which had produced intratracheal invasion. **Louis Clerf**, Philadelphia, discussed a similar case of tracheal obstruction and stressed the importance of an esophageal study in such cases to determine the relative fixation of an obstructing mass during swallowing. The case reported by Clerf proved to be a retrosternal thyroid, not palpably attached to a small adenoma in the neck.

**Maurice Bonnier, Montreal, Quebec: Some Interesting Endoscopic Foreign Body Cases.**—Bonnier reported three unusual foreign bodies in the air and food passages which were removed endoscopically. The first was a corset bone  $8\frac{1}{2}$  inches in length which was lodged in the distal esophagus and stomach; the second, a tubular portion of a No. 5 tracheotomy tube in the right main bronchus; and the third an open safety pin present in the right lower lobe bronchus for ten years, unsuspected until hemoptysis led to a roentgen examination.

**Burt R. Shurly, Detroit: A Foreign Body Retained Thirteen Years in the Bronchus.**—Shurly reviewed the antituberculosis survey which had been carried on by the Detroit public schools for the past number of years. Originally this consisted of tuberculin tests of all school children followed by roentgen examinations of the chest in tuberculin positive cases. Now by the use of 35 mm. film all children are x-rayed, and the tuberculin tests have been discontinued. Thus pulmonary lesions other than those of tuberculosis are discovered. In one instance, a 17-year old boy was found to have a foreign body, a screw, in the right lower lobe bronchus. The history was elicited from his surprised mother that he had "swallowed a nail at the age of four." She insisted there had been no symptoms at that time nor since that time and ignored the accident. The suggested endoscopic removal was ignored by the patient and his family.

**G. W. Grier, Pittsburgh: Mediastinal Enlargement in Acute Laryngotracheobronchitis.**—Grier discussed the x-ray findings in 59 of a series of 129 cases of laryngotracheobronchitis that had had x-ray examinations of the chest; 34 of these showed a widening of the superior mediastinal shadow in the x-ray film which was apparently due to an enlargement of the paratracheal lymph glands, associated with some inflammatory swelling of the surrounding tissue. These shadows were characterized by a definite widening of the upper mediastinum with a bilateral, concave outer margin. In a few cases which had been followed the enlargement disappeared spontaneously and in one case films made prior to the onset of the acute laryngotracheobronchitis were negative. The condition was also observed in bronchopneumonia. It was differentiated from the x-ray appearance of an enlarged thymus or other mediastinal tumors by the fact that such tumors present a convex border of the mediastinal shadows. Occasional cases of congenital heart disease show a widening of the mediastinal shadow, but these may be differentiated readily by the configuration of the heart.

**Julian Johnson, Philadelphia: Surgical Treatment of Carcinoma of the Esophagus.**—Johnson reported a case of a 57 year old man who consulted his physician four weeks after noting some difficulty in swallowing. A carcinoma of the mid esophagus was found on x-ray examination and on esophagoscopy. Following a preliminary gastrostomy, a total excision of the thoracic esophagus was done. There was no evidence of metastases. At the present time the patient is back at work, six months following the operation, using an artificial esophagus in order that he may eat by mouth. He is able to eat a normal diet. The artificial esophagus consists of a rubber tube attached to the superior esophageal stump, leading externally to the gastrostomy opening. An ingenious part of this artificial esophagus consists of a rubber balloon midway along its course to permit the normal, rather rapid swallowing of food. A small gas outlet relieves overdistention of this bag satisfactorily. Johnson stressed the fact that in this case the patient consulted his physician four weeks following the first symptoms and the esophagotomy was completed seven weeks following the first symptom. The paper was discussed by **Henry B. Orton, Newark, N. J.**, who pointed out that such early operations could be made only if roentgenologists realized the importance of beginning the study of the gastrointestinal tract at the mouth rather than at the stomach.

William Hudson, Detroit, Richard Overholt, Boston, and Waitman Zinn, Baltimore, presented cases of surgical removal of the esophagus, stressing, with Johnson, the feasibility of this procedure.

Herman J. Moersch, Rochester, Minn. **Further Observations on the Treatment of Esophageal Varices by Injection of a Sclerosing Solution.**—Moersch discussed the etiology and suggested therapy of esophageal varices, pointing out that none of the methods of therapy has proved entirely satisfactory. He had attempted unsuccessfully to produce varices in animals in order to evaluate experimentally various methods of therapy. Using an esophagoscope with both proximal and distal illumination, Moersch began the injection of varices using sodium morrhuate solution 2.5 per cent, injected into the varix by a long, specially constructed needle. At the present time he uses a 5 per cent solution, obtaining a better and more rapid sclerosis. The technique of the injection consists of esophagoscopy exposure of the varicose vein, followed by the application of pressure to the proximal end of the vein with the lip of the esophagoscope. The needle is then inserted into the vein, the needle having been previously filled with a solution of sodium citrate. Certainty that the needle is in the vein is obtained by withdrawal of blood into the syringe. If the patient complains of pain during the procedure, the injection is discontinued at once. Approximately 5 to 7 cc are injected twice per week. Eight injections are made, followed by a rest period of about three months. A review of the results obtained by Moersch in the treatment of eleven patients with varices of the esophagus was presented. Six patients had had previous splenectomies with massive hemorrhages. Three to fourteen injections were given these patients and the number of hemorrhages was markedly reduced. The number and severity of the hemorrhages were reduced in all cases and the general health of the patients as a group was considerably improved. However, Moersch felt sufficient time had not elapsed to draw definite conclusions as to the efficacy of the procedure. The paper was discussed by C. L. Jackson, Philadelphia, who presented two additional cases similarly injected, one an 8 year old girl with Banti's disease who had had a splenectomy. Three injections had been made. The second, an adult, had varices which extended the entire length of the esophagus. He had also had a splenectomy. Edward Benedict, Boston, likewise presented one case in which twelve injections had already been made.

Hugh G. Beatty and Dwight Palmer (by invitation), Columbus, Ohio. **Esophageal Neuroses.**—Beatty and Palmer gave a brief presentation of a class of patients exhibiting functional difficulties in swallowing certain types of food or medication. They pointed out that these patients are quite numerous and that they are not all of a typical neurotic type. They usually do not have a history of trauma nor do they have a structural change in the esophagus. This particular syndrome is unassociated with spasm of the upper or lower ends of the esophagus. They stressed the importance of the direct esophagoscopy examination of these patients, both for diagnosis and therapy, and suggested a very limited use of anesthesia for the procedure. Psychotherapy alone was felt to be insufficient for the treatment of these cases, and training in the swallowing act was considered essential. Porter Vinson, Richmond, Va., pointed out the systemic effects of a very improper diet which occur occasionally in hysterical individuals who have difficulty in swallowing, since they do not or cannot eat meat and other essential foods for a balanced diet.

Edward Benedict, Boston. **Carcinoma of the Esophagus With Special Reference to Treatment by Radical Surgery, X-ray, and Bouginage.**—Benedict discussed the various forms of radical surgery and the palliative treatments which were



used in 55 cases of carcinoma of the esophagus. In 10 of the cases the esophagus was removed, 3 were explored and found to be inoperable, and 1 died of a post-operative complication. A gastrostomy was performed in 7 cases, 8 were untreated, 26 were treated by deep x-ray therapy, some with and some without bouginage. Of the surgical cases, 2 of the carcinomas were in the cervical esophagus; on exploration both were found to be inoperable. Of 5 patients operated upon in whom the lesion was in the thoracic esophagus, 1 is living and well after two years, having had a Grade 2 carcinoma. A second patient of approximately the same duration in whom the thoracic esophagus was removed are living and well, but the duration of time following surgery is insufficient to consider them surgical cures. Benedict stressed the use of the peritoneoscope to rule out liver metastases prior to surgical exploration of the thorax. In carcinomas of the lower esophagus, the transthoracic approach was used, the lower esophagus and upper portion of the stomach being removed. Of 5 of these transthoracic esophagogastricectomies, 1 is living after one and one-half years without recurrence, having had a Grade 2 carcinoma. A second is living and well, after about the same duration, having had a Grade 3 carcinoma. In the other 3 of these patients the carcinomas were found to arise in the upper portion of the stomach and extend into the submucosa of the esophagus; esophagoscopic biopsies were negative in these cases. One of these 3 patients died postoperatively; the other 2 are living and well although only a short period of time has elapsed since surgery. In the cases of palliative treatment, Benedict considered x-ray therapy and bouginage through the esophagoscope to be the method of choice. Of the 14 patients treated in this manner, 10 tolerated treatment well and 4 did not. There were no perforations or other accidents in this series. Benedict stated that he avoided gastrostomy in these cases to as great an extent as possible.

Paul Holinger, Chicago, advocated early gastrostomy both for increasing the patient's general well-being by increasing his food intake and for aiding in certain therapeutic procedures. Porter Vinson, Richmond, Va., stated that effective dilatation depends on the size of the sound and felt that dilatation through the esophagoscope was insufficient to give these patients relief. He stated that the use of pneumatic bags is more satisfactory for these patients but that if the recurrent laryngeal nerve is involved little benefit is derived from dilatation. Gabriel Tucker, Philadelphia, pointed out the fact that carcinoma of the upper third of the esophagus responds well to irradiation, giving the patient one and one half to three years of life with a normal swallowing function. He disagreed with Benedict, stating that an early gastrostomy and less actual trauma to the tumor itself by dilatation is a preferable procedure. A. Ayala, Mexico City, Mexico, discussed the advantage of an early gastrostomy in esophageal carcinoma. He referred to several cases of surgical removal of the esophagus which he had performed successfully. Herman Moersch, Rochester, Minn., pointed out that in a large series of cases of carcinoma of the esophagus the life expectancy was the same with either dilatation or gastrostomy. He presented 1 case of a patient with an inoperable carcinoma of the esophagus in whom palliative diathermy had been used. The patient is still living six years following this procedure, but a recurrence has recently been diagnosed. Louis Clerf, Philadelphia, pointed out that since the results of irradiation change so constantly from year to year and are showing steady improvement, these may be relied upon more in the future. Richard Overholt, Boston, presented 5 cases of esophagectomy with postoperative deaths in the first 2 and a fatal recurrence of the carcinoma in the third and fourth cases after one year; the last patient is living and well, six months following the esophagectomy. William Hudson, Detroit, presented 1 case of a carcinoma of the esophagus in which a urethral resectoscope had been used to remove portions of the tumor with satisfactory palliative results.

**Chevalier L. Jackson and Frank W. Konzelmann** (by invitation), Philadelphia: **So-Called Adenoma of the Bronchus.**—Jackson and Konzelmann presented the endoscopic findings and histology of this important group of bronchial tumors which is coming to be widely recognized as a clinical and pathologic entity. These tumors have some of the pathologic characteristics of low-grade carcinomas and may occasionally undergo malignant change. However, because of their cellular structure and their apparent incapacity to infiltrate or metastasize, they indicate a relatively benign character. They feel that many of the "inflammatory tumors," polyps, hemangiomas, fibromas, etc., in the literature could be classed with the "adenomas" pathologically and clinically. Of special interest in this report is the fact that it gives the present status of a series of 12 cases of bronchial tumor thought to be of this type reported by Jackson and Konzelmann five years ago. Three of the 12 have now been recognized as low-grade adenocarcinomas, with histologic characteristics which in retrospect distinguish them from the other 9. In discussing the therapy, they stated that bronchoscopic treatment is effectual in most cases of benign adenoma and other benign bronchial tumors, but often a number of treatments are required and in some cases it seems impossible to obtain a complete and permanent cure such as will make subsequent treatment unnecessary. In view of the definitely benign character of these tumors, and the excellent results obtained by conservative treatment, it would seem that it should be given a trial in every case, but surgical treatment of more radical character may be justifiable in some of the cases.

**Alfred Goldman**, San Francisco, presented a series of 19 similar cases of which 5 became malignant. He felt that bronchoscopic therapy was indicated for drainage only in these cases, and that if not soon successful, lobectomy was indicated. **Edward Benedict**, Boston, stated that in a series of 27 cases no cures had resulted from bronchoscopic removal alone. Six were symptom-free following removal of the tumor, but the tumor had recurred in each case. One patient who refused treatment remained symptom-free. Eleven of the cases developed an empyema. Eight had sufficient lung damage to require lobectomy, and 5 sufficient to require pneumonectomy. Three of the patients died of the tumor because of lung gangrene or hemorrhage. **Louis Clerf**, Philadelphia, mentioned the fact that not all of these tumors grow with the same rapidity. One of his patients whose original biopsy showed an endobronchial tumor with acini typical of an adenoma died three years later and the tumor was definitely a squamous-cell carcinoma.

**Paul Holinger**, Chicago, and **Ralph Rigby**, Council, Idaho (by invitation): **Bronchogenic Carcinoma Without Bronchial Obstruction.**—Holinger and Rigby presented 3 cases of bronchogenic carcinoma that were characterized clinically simply by a nonproductive cough and x-ray evidence of an extensive bilateral infiltrative process unassociated with bronchial obstruction or bronchial erosion. The roentgen findings in 2 of the cases were characteristic of those of fungus disease of the lungs. Post-mortem examination in each case revealed small primary lesions whose actual site was difficult to establish, with extensive metastatic spread of the carcinoma cells throughout both lungs. The invasion was by way of the peribronchial and perivascular lymphatics in each case without erosion of the walls. In none of the cases were the distant metastases significant.

The paper was discussed by **Richard Overholt**, Boston, who presented the problem of diagnosis of bronchogenic carcinoma when bronchoscopic evidence of neoplastic disease is absent. He stressed the value of exploratory thoracotomy in questionable cases and gave statistical evidence to support the value of such a procedure. The percentage of cases of bronchogenic carcinoma salvaged in his series was highest in those cases in which the diagnosis could not be made by simple bronchoscopic removal of tissue for biopsy.

# REPORT OF THE MEETING OF THE AMERICAN ASSOCIATION FOR THORACIC SURGERY, JUNE 9-11, 1941, TORONTO, ONTARIO

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OVER 200 members and guests registered for the meeting at which thirty-one papers were read.

The first morning session was concerned with treatment of pulmonary tuberculosis by thoracoplasty. Oscar Auerbach, Staten Island, N. Y., discussed the anatomic changes in the lungs following thoracoplasty. Of 134 cases studied at autopsy, cavity closure had occurred in 17 cases. Bronchi showed tuberculous changes only in the bronchocavitary region; emphysema was found consistently in the contralateral lung.

Ralph Adams and Paul DuFault, Boston, reported the results of surgical therapy for pulmonary tuberculosis at one sanitarium over a thirteen-year period. Two hundred forty-one patients were treated by thoracoplasty and 19 by extrapleural pneumothorax. The rate of conversion was 81 per cent. The all-inclusive death rate was 16 per cent.

George F. Skinner, St. Johns, New Brunswick, presented results in two series of patients with pulmonary tuberculosis treated with thoracoplasty. One series was operated upon more than ten years ago, the other more than five years ago but less than ten years ago. The later series showed a lower mortality (6.35 per cent) despite the more frequent performance of apicolysis. The results in this series were also better, 65 per cent "good results" as opposed to 50 per cent.

Richard H. Dieffenbach and Anthony D. Crecca, Newark, N. J., analyzed the results in 100 consecutive cases of thoracoplasty on which 221 operative procedures were performed without a death. Seventy-one cases were rendered sputum negative. Pentothal and a combination of oxygen and nitrous oxide were satisfactory anesthetics. A vegetable oil tried in a few cases of extrapleural pneumolysis was reported to be satisfactory.

George G. Finney, Baltimore, analyzed 104 cases of thoracoplasty for pulmonary tuberculosis. The value of routine blood transfusion during the operation and the use of an axillary pillow to decrease the effort of breathing were stressed. Sixty-two and five-tenths per cent of the patients were classified as arrested or apparently arrested after operation. There were 6 operative deaths and 13 nonoperative deaths. There were 25 wound infections.

H. Meltzer, Ninette, Manitoba, reported the results of thoracoplasty in 180 cases of pulmonary tuberculosis. It was shown that the results in well-selected patients over 10 years of age were as satisfactory as those in the younger age groups. Seventy-nine per cent of the patients became sputum negative after the operation.

A. M. Vineberg, D. Ackman, and M. Aronovitch, Montreal, Quebec, discussed the results of unilateral thoracoplasty in the presence of bilateral pulmonary tuber-

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**Chevalier L. Jackson and Frank W. Konzelmann** (by invitation), Philadelphia: **So-Called Adenoma of the Bronchus.**—Jackson and Konzelmann presented the endoscopic findings and histology of this important group of bronchial tumors which is coming to be widely recognized as a clinical and pathologic entity. These tumors have some of the pathologic characteristics of low-grade carcinomas and may occasionally undergo malignant change. However, because of their cellular structure and their apparent incapacity to infiltrate or metastasize, they indicate a relatively benign character. They feel that many of the "inflammatory tumors," polyps, hemangiomas, fibromas, etc., in the literature could be classed with the "adenomas" pathologically and clinically. Of special interest in this report is the fact that it gives the present status of a series of 12 cases of bronchial tumor thought to be of this type reported by Jackson and Konzelmann five years ago. Three of the 12 have now been recognized as low-grade adenocarcinomas, with histologic characteristics which in retrospect distinguish them from the other 9. In discussing the therapy, they stated that bronchoscopic treatment is effectual in most cases of benign adenoma and other benign bronchial tumors, but often a number of treatments are required and in some cases it seems impossible to obtain a complete and permanent cure such as will make subsequent treatment unnecessary. In view of the definitely benign character of these tumors, and the excellent results obtained by conservative treatment, it would seem that it should be given a trial in every case, but surgical treatment of more radical character may be justifiable in some of the cases.

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obtained when one lung was made to respire pure nitrogen. In their opinion, fluoroscopy combined with roentgenography gives a fairly accurate estimation of the functional capacity of the lungs.

J. M. Chamberlain, Oneonta, N. Y., reviewed 100 consecutive cases of endobronchial tuberculosis. Pneumothorax appeared to be a dangerous procedure in this condition since one-third of the patients so treated died. Thoracoplasty was the best available method of treatment. In selected cases pneumonectomy or cavity drainage might be employed.

W. M. Tuttle, Detroit, outlined his experience with tuberculous stenosis of the major bronchi in 105 patients. In 30 cases, thoracoplasty was performed without a death. When a stenosis of a major bronchus occluded one-half the lumen, a thoracoplasty was indicated. Stenoses of small bronchi might be treated with pneumothorax. Results of local treatment with silver nitrate were disappointing.

The second morning session was opened by J. Alexander, Ann Arbor, Mich., who presented a paper on the effect of thoracoplasty upon pulmonary tuberculosis complicated by stenotic tuberculous bronchitis. His experience over a period of seven years led him to the conclusion that thoracoplasty in selected cases was a safe and worth-while procedure. Thoracoplasty was indicated if the patient could expectorate, but if expectoration was impossible, pneumonectomy was indicated if there were signs of toxemia.

In discussing the three papers on bronchial stenosis, E. J. O'Brien, Detroit, said that every patient should probably be bronchoscoped before attempting pneumothorax as well as before thoracoplasty. Cavernostomy was suggested as a possible substitute for pneumonectomy in selected cases with stenosis. J. D. Steele, Milwaukee, Wis., pointed out that all stenoses were not permanent and advised caution in subjecting such patients to major surgical procedures. E. F. Butler, Ithaca, N. Y., discussed the indications for performing a pneumonectomy for pulmonary tuberculosis. In his opinion, thoracoplasty should always precede pneumonectomy in order to prevent an overdistention of the remaining lung. Pneumonectomy could be done provided all the active tuberculous infection would be removed; if the pleura was not involved; if the bronchi was normal at the point of transection and if the opposite lung was able to carry on the entire respiratory function. F. S. Dolley, Los Angeles, felt that thoracoplasty should always precede pneumonectomy for tuberculosis since it might improve the patient's condition to such an extent that pneumonectomy would not be necessary. In any event, the pleural space would be much smaller if a tuberculous empyema developed after excision of the lung. He recommended that in cases with stenosis if the sputum became negative but bronchiectasis remained, the involved pulmonary tissue should be excised.

L. R. Davidson, New York City, reported on some investigative procedures regarding the closure of refractory and residual cavities. The residual post-thoracoplasty cavity was treated by a two-stage operation including pneumonostomy and the use of a pedicle muscle flap. The large medially located primary cavity was treated by thoracoplasty, the Monaldi procedure, or a combination of these two procedures. The large peripheral cavity was treated by the Monaldi technique followed by cauterization of the bronchus. If large cavities are associated with bronchiectasis, pneumonectomy or lobectomy must be considered.

W. L. Rogers, S. J. Shipman, and A. C. Daniels, San Francisco, described their method of dealing with residual cavities after thoracoplasty. The type of

culosis. In a series of 50 cases, the results were best in those in which the disease in the contralateral lung showed evidence of active retrogression.

A. H. Aufses, New York City, reported the results in 90 consecutive thoracoplasties for pulmonary tuberculosis. Seventy per cent of the patients had their disease arrested, 19 per cent did not. Six and five-tenths per cent of the patients died shortly after operation; 4.5 per cent of the patients died from causes unassociated with the immediate effects of the operation.

C. P. Bailey, Philadelphia, presented a preliminary report on 19 patients with extraperiosteal pneumonolysis for pulmonary tuberculosis. The space created is maintained by refills of air. Up to ten ribs may be stripped at one time. The denuded ribs are left in place and paradoxical breathing does not occur.

The preceding papers were discussed together. J. Alexander, Ann Arbor, Mich., felt that it was difficult to evaluate the factors making for good results in thoracoplasty. The value of routinely doing an apicectomy was thought to be very doubtful, and that it probably should be performed only in a minority of cases. He recommended that only two ribs be removed at one time to achieve the lowest possible mortality. H. Lilienthal, New York City, stated that the cough reflex should not be abolished either during or after thoracoplasty. F. S. Johns, Richmond, Va., felt that the anesthetist was much more important than the anesthesia in the results obtained after thoracoplasty. H. E. Decker, Pittsburgh, Pa., pointed out that the serious wound infections came from the pleura and were putrid in character. He felt that the blocking of the afferent nerve impulses by novocain was the most important factor in reducing the shock associated with thoracoplasty. R. H. Overholt, Brookline, Mass., stated that he had followed 107 patients who had undergone thoracoplasty over five years ago, and found 95 per cent of them to be alive. L. R. Davidson, New York City, advised that thoracoplasty not be done unless the disease in the contralateral lung is under control. He felt that empyemas in which a mixed infection was present should be treated by drainage and unroofing. Thoracoplasty was not advisable for these cases. The Semm apicectomy was dangerous if employed routinely. A. D. Creech, Newark, N. J., pointed out that Bailey's operation would avoid scoliosis in children and that it might also be valuable in patients with acute pulmonary processes. R. H. Meade, Jr., Philadelphia, reported 6 cases operated upon by a modification of Bailey's operation.

The first afternoon session was opened by M. Pinner, G. Leiner, and W. A. Zavod, New York City, who reported their studies of the functional capacity of re-expanded lungs following pneumothorax and of lungs following thoracoplasty as determined by bronchspirometry. One hundred seventy tests were performed on 130 patients. It was conclusively demonstrated that roentgenography is not able to differentiate those patients who have considerable disturbance of their respiratory physiology due to pleural pathology.

W. Whitehead, Detroit, described a new technique for the study of respiratory physiology by bronchspirometry. An open circuit with air and low oxygen mixtures was employed. This method gives more complete information. Lungs can be put under stress at will by having one respire low oxygen mixtures and the other, air or high oxygen mixtures.

G. W. Wright and W. Woodruff, Saranac Lake, N. Y., discussed the results of their studies in bronchspirometry. Their chief concern was determining the results

The second afternoon session was started with the presidential address by F. B. Gurd, Montreal, Quebec. The president outlined a method of treating pulmonary abscesses with a salve composed of bismuth, iodoform, and petrolatum applied locally and with packing after the abscess has first been opened by operation. A technique by which muscle flaps could be used to fill an abscess cavity was also delineated.

R. R. Shaw, Dallas, Tex., presented an excellent paper on the treatment of pulmonary abscess. Early surgical drainage was advocated. Figures were presented which showed definitely that surgery could accomplish more cures with a lower mortality than conservative treatment. Twenty patients with single pulmonary abscesses treated surgically had a mortality of 5 per cent. Thirteen patients with multiple abscesses had a 30 per cent mortality. Eight patients treated within six weeks after abscess developed had no mortality. Nine patients treated between six weeks and six months after abscess developed had an 11 per cent mortality. Sixteen patients treated six months or longer after abscess developed had a 25 per cent mortality.

In the discussion of Shaw's paper, H. Neuhof, New York City, reported 127 cases of acute lung abscess treated surgically with only 4 deaths. The injection of methylene blue and lipiodol in the intercostal space combined with roentgen examinations was recommended as of great aid in locating the optimum point for drainage.

A. O. Singleton, Galveston, Tex., presented a study of 200 consecutive cases of thoracic empyema. Six of 170 cases of empyema treated primarily at the author's clinic resulted in chronic empyema. Twenty-eight chronic empyemas were treated. Twenty-three were cured; 5 died.

In the discussion of Singleton's paper, F. B. Gurd, Montreal, Quebec, pointed out that the widespread use of the sulfonamides in the treatment of pneumonia was now a factor in delaying drainage of empyemas since these drugs frequently cause an acute empyema to be asymptomatic.

A. L. Loekwood, Toronto, Ontario, discussed surgery of the chest in war. The need of chest and abdominal armor for soldiers in the present war was emphasized.

At the annual dinner at the Royal York Hotel, some 200 members and guests of the Association enjoyed a very British and very delicious banquet. Toasts were drunk to the King and to the President. Wing Commander G. E. Hall, R.C.A.F., at the conclusion of the banquet, related some of the many new problems now being faced by physicians in the Royal Canadian Air Force.

The last morning session was opened by A. L. Brown and W. Brock, San Francisco, who described a method of treatment of large pulmonary air cysts (balloon cysts) by an endoentaneous flap. In brief, the method recommended was drainage for several months by means of an Eloesser type of skin flap. Roentgenograms of several successfully treated cases were shown.

In the discussion of this paper, C. Haight, Ann Arbor, Mich., pointed out that a large number of these balloon-type cysts were associated with an anomalous artery coming from or through the diaphragm and entering the lower lobe of the lung. R. Douglass, Ithaca, N. Y., and E. W. Davis, Washington, D. C., confirmed this statement of Haight's.

cavity was first studied by measuring the intracavitary pressure. In suitable cases, the cavity was opened and a skin flap employed to obliterate it.

The second morning session was opened by A. Ochsner and M. E. DeBakey, New Orleans, who discussed the surgical significance of metastasis in primary carcinoma of the lung. Two cases with metastases in the axillary lymph nodes were reported. It was felt that these metastases occurred through lymphatics running across the pleural space in adhesions. The possibility of metastases in the lymph nodes of the opposite side of the mediastinum was also pointed out.

H. Neuhof, C. B. Rabin, and I. A. Sarot, New York City, discussed a topographic classification of cancer of the lung with special reference to the surgical implications of the circumscribed variety. These authors felt that tumors which by roentgen examination appeared to be circumscribed were much more apt to be operable for lymph node involvement was much less frequent in this type of tumor.

A. W. Harrington, Rochester, Minn., related his experience in the performance of pneumonectomy for carcinoma of the lung. All of his cases are drained in the fourth intercostal space in the midaxillary line. The surgical mortality was 33 $\frac{1}{3}$  per cent. The mortality of exploration was 15 per cent.

N. S. Shenstone, Toronto, Ontario, presented the results of total pneumonectomy for carcinoma, bronchial adenoma, and inflammatory conditions of the lung performed at the Toronto General Hospital during the past four years. In addition, a description of the method used in dealing with the hilar structures was given.

The four preceding papers were discussed as a unit.

E. A. Graham, St. Louis, reported a 25 per cent operative mortality in a series of 20 total pneumonectomies for carcinoma of the lung performed since Jan. 1, 1940. He felt that a diagnosis could be made in 75 per cent of the cases when the carcinoma was still operable. As he saw it, the chief problem at the present time was in educating the public to consult physicians early. The contraindications to total pneumonectomy were as follows: (1) presence of distant metastases; (2) the presence of pleural fluid; (3) involvement of the brachial plexus, the phrenic nerve, or the recurrent laryngeal nerve; (4) fixation of the hilus as determined by bronchoscopy. W. F. Riehoff, Jr., Baltimore, reported a 25 per cent operative mortality in a series of 55 patients upon whom total pneumonectomy was performed for carcinoma of the lungs. Twenty five per cent of these patients had had the bronchus open up after pneumonectomy. This experience occasioned an experimental study on dogs to determine how a bronchus closed with sutures healed. In 50 dogs, the cut end of the bronchus was covered over with a flap of pleura and none reopened. R. H. Overholt, Brookline, Mass., stated that his operative mortality for total pneumonectomy for carcinoma of the lung was now 25 per cent. E. D. Churchill, Boston, stated that in his opinion a histologic classification of lung carcinomas would be much more valuable than a topographical classification.

This session was completed by a paper read by C. W. Lester, A. Cournand, and R. L. Riley, New York City, concerning the effect of pneumonectomy in children on pulmonary function. Four children under 14 years of age were studied for from one and one half to three and one half years after pneumonectomy. The single remaining lung showed no evidence of emphysema. The lung volume and maximum breathing capacity, however, were above normal for one lung. Gas exchange was efficiently managed.



Philadelphia. It was shown that fairly large transfusions would produce pulmonary congestion and edema in cats after lobectomy, but that transfusions of equal size produced no ill effects in normal cats. This effect was thought to be due to the sudden decrease in the vascular bed of the pulmonary tissue.

The Ross Lambert Prize Essay was read by C. A. Moyer, Boston. The title of this paper was *Major Changes in the Fundamental Relationships of the Respiratory Drive Mechanisms During Evipal and Pentothal Anesthesia, With Special Consideration of Possible Applications to Transpleural Surgery*. Convincing evidence was brought forward to show that the respiratory mechanism reacted in quite a different manner to various stimuli when under the influence of evipal or pentothal anesthesia.

The last paper of the meeting was presented by J. R. Paine, Minneapolis, Minn., on observations of the effects of the prolonged administration of high oxygen concentrations to dogs. It was shown that the respiration of an oxygen concentration of over 80 per cent produced in time changes in the lungs, liver, and spleen of dogs; death might ensue. It was also shown that the respiration of a high oxygen concentration altered both the quality and quantity of the gas contained in the intestinal tract.

Thirteen additional papers were read by title.

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## REVIEW OF THE MEETING OF THE AMERICAN ORTHOPEDIC ASSOCIATION, FIFTY-FIFTH ANNUAL SESSION, JUNE 9-12, 1941. TORONTO, ONTARIO

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*(From the Department of Surgery, School of Medicine, Tulane University)*

THE Fifty-Fifth Annual Session of the American Orthopedic Association was held in Toronto, Ontario, extending through four days, from June 9 to June 12. An extremely interesting series of clinical demonstrations were presented by the local group of surgeons.

The first day of the meeting was devoted almost entirely to clinical reports and case presentations. A. D. McLachlin, Toronto, presented a series of 28 cases of simple bone cyst, which had been treated and followed up over a period of several years. He re-emphasized the fact that the best results were to be obtained by adequate curettage and the implantation of bone chips, or a graft following surgery.

F. R. Wilkinson, Toronto, presented a series of 11 cases of acute hematogenous osteomyelitis treated during the past two years. In 10 cases a staphylococcus was recovered, in 3 a streptococcus, and in 1 an influenza bacillus. The general plan of treatment afforded immobilization, treatment of the fluid balance, blood transfusions, and sulfathiazole given orally as a general rule, but intravenously when indicated in sufficient amounts to raise the blood level to approximately 5 mg. per cent. As soon as the general condition of the patient would permit, and once the diagnosis was made that pus was present in the subperiosteal space, operation was decided upon. This could ordinarily be done within twenty-four

H. B. Stephens, San Francisco, reviewed 19 cases of patients with cancer of the thoracic esophagus and the upper end of the stomach who were subjected to surgical exploration. Of these patients, all operated upon since 1937, 4 are still alive. In only 1 of the 1 surviving is life expectancy good. It was recommended that if necessary for removal of a cancer of the esophagus, the aorta could be mobilized and retracted by the ligation of several pairs of intercostal arteries.

D. B. Phemister, Chicago, described his experiences in the resection of the esophagus for carcinoma in 8 cases. He recommended that in such cases no preliminary gastrotomy be performed. That portion of the esophagus remaining attached to the stomach, if brought out to the skin, serves the purpose of the gastrotomy much better.

H. W. Wookey, Toronto, Ontario, discussed his technique for dealing with malignant lesions of the cervical portion of the esophagus. In several instances, he has been able to remove the growth and reconstruct the esophagus with a skin flap from the neck.

B. N. Carter, O. A. Abbott, and C. R. Hanlon, Cincinnati, Ohio, described the results of their experimental study of tubes made from the greater curvature of the stomach. Two series of dogs were used. In one the tube was brought through the thoracic cavity. In the other, the tube was placed without the thorax beneath the skin. The latter procedure seemed the more satisfactory.

During the discussion of the four preceding papers, E. D. Churchill, Boston, stated that patients, for whom resection of the esophagus was contemplated, should all be bronchoscoped first to determine whether or not the left main bronchus was uninvolved by the carcinoma. He favored the approach through the left side of the chest with mobilization of the arch of the aorta. Other discussers brought out the fact that skin tubes for reconstruction of a removed esophagus could be made to unite satisfactorily with the mucous membrane of the esophagus but not with that of the stomach.

The first paper of the last session of the meeting was by J. Tannenberg and M. Pinner, New York City. On the basis of experimental and clinical observations, these authors drew the conclusion that bronchiectasis was due to incomplete bronchial obstruction. As a corollary, therefore, atelectasis had little or no part in its etiology.

F. Albritten, J. B. Fleck, and J. H. Gibbon, Jr., Philadelphia, discussed the use of sulfanilamide in resection of the lung. The concentration of sulfanilamide in the pleural fluid was found to parallel closely that in the blood. When used by mouth or locally, sulfanilamide was found to delay the onset and decrease the severity of the infection following lobectomy or pneumonectomy.

In the discussion of this paper, E. A. Graham, St. Louis, said that, in his experience, the use of sulfanilamide had been ineffectual in influencing the onset or course of infection following lobectomy or pneumonectomy. R. H. Mead, Philadelphia, brought out the fact that some men had insufflated sulfanilamide into the bronchi prior to lobectomy or pneumonectomy. He also reported measurements of the amount of the drug present in the bronchial secretions of patients receiving sulfanilamide by mouth. These showed that only a small proportion of the drug was excreted in this manner.

An experimental study of the effect on the cardiorespiratory function of blood transfusion following lobectomy in the cat was reported by J. H. Gibbon, Jr.,

imately ten days are allowed during which the patient becomes adjusted to the position and correction is gradually increased. During this time the patient is suspended daily for gradually increasing periods of time, until it is felt that the position can be maintained for a period of time sufficient to allow the application of a plaster cast. The cast is applied incorporating the head and the lower extremity on the convex side of the curve. Sponge rubber is used for padding. Le Mesurier feels that the method shortens the period of hospitalization decidedly and prevents complications such as pressure areas, etc., so frequently encountered with the use of the Risser jacket. In certain instances the method may not obtain quite as complete correction as might be obtained with a Risser jacket, but he claims that any difference that might be noted between the amount of correction obtained by his method and that obtained with the use of a Risser jacket was negligible.

The possibility of developing a brachial palsy, because of the acute flexion of the neck, should be carefully watched for, since several instances of this complication were reported, none of which however proved serious.

D. E. Robertson, Toronto, showed a small series of patients with Raynaud's disease and thromboangiitis obliterans treated by lumbar sympathectomy, all of whom had definite improvement in their peripheral circulatory symptoms following the procedure. He advocated the procedure as a very satisfactory method of treatment for the severe and annoying symptoms so frequently encountered in the care of these particular diseases.

The following papers were presented on Tuesday, June 10:

R. I. Harris, Toronto, discussed the etiology and pathology of fat embolism, presenting several case records which he had observed personally and several which he had collected from colleagues practicing in the local area. The importance of this disease entity as related to the field of orthopedic surgery was emphasized. It was pointed out that three common sites for the appearance of fat emboli were the lung, brain, and the kidney respectively. The possibility of discovering fat particles in the sputum was considered a valuable diagnostic aid. The presence of a fat droplet in any tissue was shown to be followed by the appearance of local hemorrhagic infiltration of the area. It was felt that this fact accounted for the marked drop in red blood cells and hemoglobin so frequently observed in the latter stages of the disease. It also explained the symptoms of pulmonary congestion so frequently observed. No specific treatment is known, symptomatic therapy only being available.

Harris also showed a novel modification used for removal of plasters. When the plaster is applied, a broad wire ribbon is incorporated in the plaster. When the time for removal of the cast arrives, one end of the wire ribbon is fixed, and an instrument resembling an over-size can opener fitted to the opposite end. By simply winding the one end of the ribbon, the cast is effectively cut through with the minimal amount of effort, and perfect comfort to the patient.

H. S. Coulthard, Toronto, discussed various problems arising in the care of tuberculosis of bone and joints, emphasizing the value of aspiration in the presence of a suspected paravertebral abscess. He felt that the aspiration was valuable not only from a diagnostic viewpoint, but also therapeutically since in several cases quoted he felt that paraplegia had been effectively avoided and the need for a costotransversectomy postponed.

Gordon M. Dale, Toronto, presented a most interesting demonstration of end-bearing stumps. The advantages of a Symes amputation in the lower extremity was discussed at length, and a large number of cases shown to substantiate his claims. The patients all walked well and seemed perfectly satisfied with their

hours. At operation the periosteum was incised and two drill holes made through the outer cortex of bone. The limb was again immobilized, and drug therapy and general constitutional measures continued for four weeks postoperatively. Using this general regime a mortality of 5.88 per cent was obtained, as compared with one of 20 per cent previously shown by a study of hospital records. Several additional advantages of the method were mentioned: (1) There seemed to be a definite improvement in the clinical course. (2) Less bone destruction was shown. (3) No secondary focus developed in any case.

S. A. Thomson, Toronto, discussed the treatment of clubfeet by the use of Denis-Browne splints, presenting a very interesting series of infants so treated. The method obviously was not advocated for patients beyond the infant age group. The method itself was clearly presented and demonstrated with infants under active treatment. Surprisingly good correction was obtained. Familiarity with the method would seem essential. The application of the splint at first glance might seem simple; still most careful attention to detail is necessary to obtain progressive and complete correction of the deformity. In using the splints correction of the varus deformity of the forefoot is obtained first, before any attempt is made to correct the varus of the heel. If the crossbar is too wide, the development of a knock-knee deformity may ensue. A "boot splint" is substituted as soon as complete correction is obtained, and this same splint used as a "night splint" for several months.

W. S. Keith, Toronto, presented a series of 6 cases with an ununited fracture of the odontoid process in which successful fusion had been obtained. Bone grafts from the ilium were used, shaped carefully to fit the defect between the atlas and axis, and these grafts fixed into position and held securely by means of a wire loop passed beneath the laminae of either vertebral body. The method obviates the necessity of fusion to the occiput, and thus minimizes the postoperative disability.

A. W. Farmer, Toronto, showed a large series of traumatic injuries in which skin grafting had been necessary. The methods used were more or less standard, the results exceptionally good. Farmer presented one particularly interesting case, that of a youngster, who had had an almost complete avulsion of a large flap of skin from the leg as a result of an automobile accident. Instead of attempting to resuture the flap back into position, the author completely removed the skin, then carefully prepared it by removal of all fatty and subcutaneous tissue, and used it as a Wolff graft to cover the defect. The various steps of the procedure were shown in a motion picture film. The end result was shown and was evident proof of the value of the procedure.

J. L. McDonald, Toronto, discussed the possibility of stimulating increased growth in the lower extremity produced by sympathectomy. Some 75 cases presenting postpoliomyelitic paralysis of a single lower extremity had been operated upon and a lumbar sympathectomy done. An adequate follow-up was available on 46 cases. It was his opinion that slight gain in the differential leg length had been obtained in 21 of these cases. The operation was justified and advocated not only upon this ground, but also because of the marked improvement in the vascular supply to the extremity.

A. B. Le Mesurier, Toronto, demonstrated a new method for obtaining correction of the primary curve in a case of idiopathic scoliosis, preparatory to spine fusion. The patient is suspended in a fishnet hammock from two overhead pulleys, being placed on the side, with the concave portion of the curve directed toward the floor. Additional aid toward obtaining correction is gained by suspension of the arm and leg on the convex side of the curve to overhead pulleys also. Approx-

lesion, and thus outline a syndrome which would clinically enable an accurate diagnosis to be made. The syndrome as outlined showed (1) an area of paraesthesia over the radial side of the forearm and thumb, (2) weakness of the triceps muscle, and (3) loss of the triceps reflex. Using this syndrome as a basis for diagnosis, several instances of isolated seventh nerve pressure have been discovered clinically, all of which have been proved subsequently by other means.

W. E. Gallie, Toronto, demonstrated a new technique for obtaining fusion of the subastragalar joint, applicable chiefly to cases which presented arthritic changes subsequent to old fractures of the os calcis. An incision is made lateral to the tendo achilles, and the subastragalar joint accurately located. A plug of bone is then removed, at least one inch in length, so as to be sure that the bone has been removed at least as far forward as the sinus tarsi. Two cortical bone grafts are removed from the adjacent tibia, and these are driven into the defect created in the subastragalar joint, with the cancellous portions of the two grafts facing together. Several cases were presented, all of which showed satisfactory bony union of the subastragalar joint with the use of this method.

An end-result study of the treatment of idiopathic scoliosis was presented by the American Orthopedic Research Committee consisting of Joseph E. Barr, Boston, Paul C. Colonna, Oklahoma City, Okla.; A. E. Shands, Jr. (Chairman), Wilmington, Del., and Lawrence Noall, New York City (Research Fellow of the Nemours Foundation). Over a year's period of time, 16 clinics were visited in various parts of the country, and a total of 425 cases studied. Whenever possible personal end-result examinations were made, and when this was impossible a careful study of the end result x-rays was substituted. A most interesting statistical review of the conclusions was presented, the details of which are to be published at an early date. In brief it was concluded that operative fusion following correction in some type of plaster apparatus gave the best results, as determined by the amount of persistent correction maintained. The amount of correction maintained where spine fusion was not resorted to was negligible. A rather high percentage of pseudoarthroses were reported in the group where spine fusion was done, 28 per cent for all types. This figure seems definitely higher than it should be. The report should provoke a good deal of interest in, and possibly improve the treatment of, idiopathic scoliosis throughout the country.

LeRoy C. Abbott, San Francisco, discussed the treatment of valgus deformity of the knee resulting from injury of the lower femoral epiphysis. He advocates a low oblique osteotomy through the femur so as to obtain an actual increase in length to compensate for the shortening due to failure of growth at the epiphysis, while at the same time affecting an accurate realignment of the femoral condyles with the tibial plateau. The defect created in the femur is filled with a wedge of bone removed from the ilium. A case showing an extreme degree of deformity was presented. Osteotomies of the femur and tibia both were necessary to obtain complete correction. An excellent result was obtained.

A statistical survey of amputations done for arterial disease at the Mayo Clinic was presented by H. B. Macey, Rochester, Minn. Two hundred and forty cases in which 261 primary amputations had been done were included in the study. A mortality of 9 per cent was reported. Gas gangrene seemed a dangerous complication encountered more frequently when an open lesion was present preoperatively. Macey believed that an amputation below the knee was preferable when possible in the presence of thromboangiitis obliterans, and Buerger's disease, even though reamputation might prove necessary at some later date. In the presence of arterial occlusion, or severe arteriosclerosis with or without diabetes, a high amputation should be done preferably. When a high amputation was done, wherever possible the site chosen was through the distal third of the femur. The

artificial limbs. The patients were all males, consequently none objected to the thickening and bulky appearance of the prosthesis just above the ankle joint. The author expressed a distinct antipathy for amputations at the level of mid-tibia, claiming that none of these stumps could stand up over a period of years, that all would eventually develop either recurrent skin infection or changes in the skin sufficiently severe to require reamputation at a later date. If a Symes amputation could not be done, Dale preferred to do a Gritti-Stokes type of amputation at the knee. A number of cases of this variety of amputation stump were also demonstrated. He expressed the belief that these two procedures afforded the ideal type of stump for an individual who would be forced to continue weight-bearing for long periods of time as part of his daily occupation. All of the patients presented were either ex-soldiers or pensioners.

G. D. W. Murray, Toronto, demonstrated and discussed the various modifications which he has recently developed for the treatment of fracture of the clavicle, Colle's fracture, and nonunion of the carpal scaphoid. In treating fractures of the clavicle in the adult, Murray uses internal fixation by means of a thin Kirschner wire passed through a drill hole on the medial end of the clavicle, and threaded through the medullary cavity of the bone, so as to thread the various fragments upon the wire, and thus obtain anatomical reduction and accurate fixation. The pin is left in place in most instances, following union. More satisfactory results are claimed, in addition to the elimination of the need for external fixation of any form.

For acromioclavicular dislocations a similar procedure is advocated. The clavicle is reduced manually, and the reduction maintained, by the insertion of two Kirschner wires, passed transversely through the acromion and into the acromial tip of the clavicle. The ends of the wires are left protruding through the skin, and these are removed at the end of five or six weeks.

The more severe types of Colle's fracture, those in which sufficient comminution is present to prevent adequate maintenance of reduction without traction, are treated by means of three wires passed vertically through the radius, the first placed in the large distal fragment or portion of this fragment, and the two remaining wires through the shaft of the radius proximal to the fracture site. The two wires proximally are used as a fixed point against which traction is exerted. An ingenious turnbuckle is applied on both the dorsal and volar aspects of the forearm, and by adjustment of these turnbuckles reduction effected.

End results studies on 57 cases of delayed and nonunion of the carpal scaphoid were presented. All had been treated by means of a tibial bone graft inserted through a quarter-inch drill hole in the body of the scaphoid. The presence of definite arthritic changes in the wrist joint was considered a contraindication to the operation. Union was obtained with the use of this technique in all but one case.

F. I. Lewis, Toronto, discussed the treatment of nonunion of fracture neck of the femur by means of a Smith-Petersen nail supplemented by a tibial bone graft. He presented a study of 26 cases so treated in which no single operative mortality had occurred. Reduction was obtained preoperatively by means of skeletal traction, then the Smith-Petersen nail was inserted so as to occupy the inferior portion of the neck, and a tibial bone graft passed through a drill hole made in the superior portion of the neck. External fixation was applied for eight to twelve weeks whenever (1) a previous nailing had been done, or (2) where an extremely short head fragment was present. The procedure was felt by Lewis to be the operation of choice since it was simple and the results most satisfactory.

K. G. McKenzie, Toronto, presented the clinical findings in a patient in whom an isolated lesion of the seventh cervical nerve was present. It was thus possible to determine accurately the type of sensory and motor changes resulting from this

developed. Oscar Miller, Charlotte, N. C., in his discussion re-emphasized the need for accurate anatomical reduction, and again stressed the fact that calcaneotibial fusion gave the best results when the astragalus had to be removed.

Philip D. Wilson, New York City, presented a paper on the treatment of compound fractures. The paper actually presented his experiences in the treatment of a series of some 74 compound fractures treated under his direction at the American Hospital in Britain, Basingstoke, England, during the past year. The vast number of these patients had been injured and had received their primary treatment elsewhere, arriving at the Park Prewett Hospital days or weeks later. In the definitive treatment of the various fractures, the "closed plaster" technique was employed by preference. In the lower extremity various forms of pin fixation were used. For fractures of the femur, the Roger-Anderson and the Haynes methods of multiple pin fixation were used. This was considered of inestimable value since it enabled the surgeon to maintain reduction and fixation of the fracture, while at the same time the plaster case could be removed and the wound dressed at will without disturbing the fracture site in the least. The Roger-Anderson method of fixation with four half pins was performed in treatment of comminuted fractures of the tibia and fibula for the same reasons. Due to difficulties encountered during the black-out it was pointed out that primary splinting at the site of fracture was in most instances found impractical. The need for properly trained personnel at the point where primary treatment was instituted was stressed. Wilson felt that very definite improvement had been noted in the character of the wounds due to the use of sulfanilamide and sulfathiazole.

During the afternoon session, the discussions were mainly formed on war subjects. Colonel George Nasmith, Toronto, told of his personal experiences in and around London while engaged in the organization and directing the activities of the Canadian Red Cross units in England.

Philip D. Wilson, New York City, described the activities and the problems encountered in the organization and operation of the American Hospital in Britain, also devoting a good bit of time to his personal observations of the types and variety of wounds encountered in modern warfare and the special problems presented by them. He reported that the American Hospital in Britain has been asked to expand its facilities and is to take charge of a new 600 bed unit in Oxford shortly.

James Ross Millar, Ottawa, Ontario, discussed his experiences with ex-soldiers since the last war, stressing particularly the problems presented by those men upon whom amputations had been necessary. He urged that the members of the Association aid in an effort to afford a more widespread dissemination of knowledge of the problems of the limb maker in fitting a prosthesis, feeling that with this knowledge more adequate stumps might be afforded at the time of the initial amputation.

Colonel Norman Kirk, Washington, D. C., George E. Bennett, Baltimore, and Guy W. Leadbetter, Washington, D. C., discussed the various steps which have been taken to organize and provide adequate orthopedic care in the United States Army.

Professor C. H. Best, Toronto, described the Canadian Project for the Preparation of Dried Human Serum for Military or Emergency Use. Blood from donors is collected in several outlying areas, brought to the central station in Toronto, and there is prepared and dried and kept in storage. The plan is operated entirely as a voluntary enterprise, the services of various types of personnel needed being so supplied. It is hoped that the idea may gradually expand elsewhere so as to afford a constant and adequate supply of dried serum for shipment overseas.

importance of care to avoid sectioning through muscle belly in performing the amputation was emphasized by Colonel Norman Kirk, Washington, D. C., in the discussion, since it was felt that this might decrease the chance for the development of gas infection. The advantages of a Gritti-Stokes type of amputation in this instance were again emphasized by G. M. Dale, Toronto, in the discussion.

The Wednesday, June 11, session included the following:

**Halford Hallock**, New York City, presented a statistical survey of the end results obtained following surgical stabilization of paralytic dislocated hips. The study was made on a group of cases so treated at the New York Orthopedic Hospital. A number of shelf operations were done, according to various techniques, but in general no improvement was noted in the limp, since the previously existent paralysis prevented stability from developing. The best results were obtained where hip fusion was resorted to. Where hip fusion is done, good stability at the knee is essential, though it is not considered absolutely essential that quadriceps power be present. In the absence of adequate strength in the quadriceps group, the ankle and foot must be stabilized in slight equinus position. Hallock concluded from his study that fusion should be advocated more frequently than the heretofore frequently used conservative measures.

Hospital treatment of chronic rheumatism was discussed by **Robert B. Osgood**, Boston. He stressed the widespread prevalence of rheumatic diseases and urged that adequate hospital facilities be made available for their treatment. Osgood felt that special hospitals should be created and endowed for the study of these diseases alone, hoping that by this means the medical profession generally could lead to a better understanding of the disease, and perhaps develop a more rational solution to the problems presented in its therapy. A unit of this type is being formed in Boston, to be incorporated in the Massachusetts General Hospital Group.

The treatment of acute osteomyelitis by the sulfathiazole drugs was discussed by **Robert Johnson**, Baltimore. In addition to general systemic treatment enough drug was administered to raise the blood level to 6 to 9 mg. per cent preoperatively. In operation in addition to incision of the periosteum a drill hole was made through the outer cortex of the bone. The decompression of the medullary cavity was emphasized as being necessary. The drug was continued for three weeks postoperatively attempting to maintain the blood level of the drug at 4 to 6 mg. per cent. No serious complications resulting from administration of the drug were noted. A decrease in the mortality and morbidity of the disease was reported. In the discussion **Rexford E. Diveley**, Kansas City, Mo., suggested that the administration of sodium sulfathiazole intravenously at times might be of definite use. He also suggested that the drug be placed locally in the wound at time of operation.

**Robert Schrock** and **Herman Johnson**, Omaha, Neb., presented a study of 13 cases of fractures and fracture-dislocations of the astragalus. The conclusions reached were: (1) Simple fractures of the astragalus should be treated simply by immobilization. (2) With displacement of the fragments, an open reduction should be done. (3) When satisfactory reposition is impossible, surgical arthrodesis is necessary. (4) Astragalectomy should not be done unless absolutely necessary. The incidence of a high percentage of aseptic necrosis following fracture of the astragalus was stressed. Where this occurred, astragalectomy was frequently necessary. A fusion of the calcaneus to the tibia following astragalectomy seemed to give the best results. In the discussion **Francis M. McKeever**, Los Angeles, pointed out that the astragaloscaphoid ligament afforded the point of entry for the main arterial supply to the astragalus, and that possibly damage to this structure might account for the high percentage of aseptic necrosis that



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James Ross Millar, Ottawa, Ontario, discussed his experiences with ex-soldiers since the last war, stressing particularly the problems presented by those men upon whom amputations had been necessary. He urged that the members of the Association aid in an effort to afford a more widespread dissemination of knowledge of the problems of the limb maker in fitting a prosthesis, feeling that with this knowledge more adequate stumps might be afforded at the time of the initial amputation.

Colonel Norman Kirk, Washington, D. C., George E. Bennett, Baltimore, and Guy W. Leadbetter, Washington, D. C., discussed the various steps which have been taken to organize and provide adequate orthopedic care in the United States Army.

Professor C. H. Best, Toronto, described the Canadian Project for the Preparation of Dried Human Serum for Military or Emergency Use. Blood from donors is collected in several outlying areas, brought to the central station in Toronto, and there is prepared and dried and kept in storage. The plan is operated entirely as a voluntary enterprise, the services of various types of personnel needed being so supplied. It is hoped that the idea may gradually expand elsewhere so as to afford a constant and adequate supply of dried serum for shipment overseas.

The meeting on Thursday, June 12, included the following:

**Lloyd T. Brown and John G. Kuhns**, Boston, discussed a paper on the extension deformities of the cervical spine. The object of this paper was to point out that as a cause of the so-called scalenus syndrome and the symptoms from cervical ribs, remote factors may be of more importance than local ones, such as an hypertrophied muscle and an hypertrophied sealenus tubercle or cervical rib. The anatomy, including the shape of the vertebrae, the ligaments and the fascia, and the muscles, is explained particularly as they are affected by positions assumed in faulty body mechanics.

The extension deformity of the cervical spine, whether it is primary or compensatory, narrows the space in the neck. It is shown that a long-standing habitual position of faulty body mechanics, because of the pull of the abdominal organs on the diaphragm and the neck, is a potential of strain on the cervical or brachial nerve plexus. Correction of these deformities not only in the cervical spine but also in the body has completely relieved not only the neurological but also the vascular symptoms associated with the scalenus syndrome and the cervical ribs.

**R. K. Ghormley and Malcolm B. Dockerty**, Rochester, Minn., gave a review of 4 cases of unusual myxomatous tumors of the knee and in conjunction with this a review of the pathology of 7 additional cases which were definitely established as cysts of semilunar cartilages.

In reviewing these 4 cases, it was their purpose to establish them either as cysts or other types of tumors. In comparing the pathology of these with the known pathology of cysts, 2 of these seemed to fall in the group of cystic semilunar tumors; 1, a large myxomatous tumor, probably did not arise in the cartilage and should be classified as paramenisal cyst and the fourth case was a true myxoma of the cartilage.

The discussion of the differentiation between so-called paramenisal cysts and true meniscal cysts and a brief review of the therapy and etiology of cysts of the semilunar cartilages were given.

**Dallas B. Phemister**, Chicago, discussed resection and transplantation in the treatment of bone sarcomas. In the past five years 8 selected cases of sarcoma of large bones were treated by massive resection and bone transplantation in an endeavor to save a useful extremity. There were 3 cases of osteogenic sarcoma, all of which were of a relatively malignant type. There were 3 of chondrosarcoma, 1 of which was relatively malignant, and the other 2 were slow growing and relatively benign. One case was a Ewing sarcoma and 1 a giant-cell sarcoma. All of the tumors began centrally except the Ewing sarcoma and had produced only slight peripheral enlargement.

One case of densely ossified osteogenic sarcoma of the upper end of the humerus was treated five years ago by excision of the humerus from the deltoid insertion upward and including the deltoid muscle, the capsule of the joint and the attachments of muscles to the greater and lesser tubercles and the posterior surface of the bone. The defect was repaired by a transplant from the tibia and the patient has remained well and worked steadily for three and one-half years as a dentist. A second case in a 12-year-old boy which was similar was treated in the same manner. However, roentgenograms taken seven weeks after operation showed evidence of local recurrence, after which an intrathoracoscupal amputation was performed. The third case of osteogenic sarcoma was of the densely ossified kind involving the upper end of the tibia. Treatment was by massive local excision of the upper four inches of bone and overlying soft parts with replacement by a double bone graft taken from the other tibia. Necrosis of the skin flap resulted in a latent infection and partial loss of the grafts. From gross examina-

tion of the specimen it looked very favorable, but microscopically there was evidence of tumor invasion of veins outside the periosteum which was of bad omen from the standpoint of occurrence of metastases. One year later there was evidence of pulmonary metastases and death occurred after one and three-fourth years.

The first case of chondrosarcoma in a girl 11 years of age was of a year's standing, involving the upper four inches of the tibia. The tumor had been partly removed six months previously. The upper five inches of the tibia was excised and a heavy transplant from the opposite tibia inserted. The graft united to the condyle of the femur and the lower fragment of tibia and subsequently hypertrophied. The patient is apparently well three years after operation and has a useful extremity.

The second case of chondrosarcoma in an 11-year-old girl involved the lower part of the shaft of the femur. It had been curetted sixteen months previously but had recurred. Fourteen centimeters of the shaft of the femur periosteum and some of the attached muscle was resected. The defect was bridged by two bone transplants from the tibia 18 cm. long and including one-half the circumference of each bone. They were fastened with two threaded wires at each end, one graft being intramedullary and the other onlaid. Union between grafts and femur took place and fourteen months after operation there is no sign of recurrence and the patient has been walking on the limb without support for four months.

The third case of chondrosarcoma in a 21-year-old woman was of five years' standing and involved the anterior portion of the upper end of the tibia. The patient refused complete excision of the upper end of the tibia and transplantation with ankylosis of the knee. Consequently a wide excision of the front and both sides of the upper end of the tibia was made and the gap partly filled out with transplants taken from the lower two-thirds of the tibia, the tibial patellar tendon being reattached with one of the transplants. The patient is free from recurrence six months after operation and has walked on the limb for the past two months. She has recovered two-thirds of normal range of motion of the joint.

The case of Ewing's tumor was in a 13-year-old boy and involved the shaft of the femur beneath the lower trochanter. Four thousand roentgen units had been administered, but roentgenograms indicated that the tumor was probably still active. With a constrictor applied over a Steinmann pin above the greater trochanter, 17 cm. of involved shaft and overlying vastus lateralis and vastus intermedius muscles were excised and the defect replaced by two bone grafts taken from the tibia as in the previous case. Infection developed and most of the bone grafts were lost. Healing was complete five months later after removal of the necrotic grafts. As there was no sign of recurrence of the Ewing tumor, which was confirmed by microscopic examination of the specimen, a heavy graft taken from the opposite regenerated tibia, was excised and inserted into the defect fourteen months after the original operation. Convalescence has been satisfactory for six weeks since operation.

The case of central giant-cell sarcoma was of the lower end of the femur in a 26-year-old man. With a constrictor applied, a biopsy was performed and while there was some question as to whether the lesion was a benign or malignant giant-cell tumor, the decision was made in favor of the latter. The lower 10 cm. of the femur, the overlying quadriceps muscle, the capsule of the joint, and the upper 1 cm. of the tibia were excised *en bloc*. Two grafts, including almost one-half of the circumference of the tibia below and about 14 cm. in length, were excised and inserted into the defect, one intramedullary and the other onlay, where they were anchored with two threaded wires at either end. Convalescence was smooth and bony union at the ends of the grafts was complete in ten weeks. It is now

seven months since operation and the patient has been walking in a caliper splint for three months without signs of recurrence.

These cases show both the advantages and disadvantages of massive bone grafting for sarcoma. Undoubtedly many early cases that are now treated by amputation would have equally good chances of survival with useful extremities if treated in this way.

In discussing a paper on femoroischial transplant, David M. Bosworth, New York City, states that in certain cases of tuberculosis of the hip and other lesions about the hip where arthrodesis is unsatisfactory or impossible, either from technical reasons or because of danger of reactivating a previous defect, it was believed that sovereignty of the femoral shaft and transplantation to the tuberosity ischium might give satisfactory results.

Nine cases of tuberculosis of the hip, 7 of them proved, in which the head and neck of the femur had been totally destroyed were operated upon with operative mortality in only 1 instance. Of the 7 cases in which the patients lived long enough to secure ankylosis, 5 became completely solid. Ankylosis in these cases between 20 and 45 degrees of flexion produce the same satisfactory gait encountered when arthrodesis of the hip is done as a primary operation. Sitting posture is likewise excellent.

The procedure is done through a lateral approach, doing an oblique osteotomy of the femur just above the level of the tuberosity of the ischium and transplanting the sharpened distal end of the femur into a gouged-out defect in the lateral portion of the tuberosity of the ischium. Maximum flexion of the thigh must be obtained and extension produced after the end of the femur is in the ischium. The procedure is difficult, much of the work must be done blind, and considerable bleeding is encountered. Some added length can usually be gained, but residual shortening due to previous disease or disability is generally present. Incastment postoperatively in a double plaster hip spica for several months is necessary. X-ray evidence of union is the guide for release from plaster.

M. N. Smith-Petersen, Boston, stated that his presentation was intended chiefly to point out the changes in technique of vitalium mold arthroplasty of the hip which have taken place since his publication of his first article. He pointed out that the incision and approach must be such as to follow anatomical planes causing the least possible damage and consequently the least possible shock. The main features about the approach have remained as described in the original publication, but experience has taught us that dividing the tendon of the direct head of the rectus occasionally gives rise to calcification of the proximal stump and this results in limitation of flexion of the hip which is most undesirable. They now detach the rectus tendon from the anterior inferior spine and suture it to the distal tendon of the gluteus minimus.

Smith-Petersen stated that in his original publication he was afraid that he belittled the efficient shaping of the acetabulum. Experience has taught him that shaping the acetabulum so that the vitalium mold will move very freely is of great importance. The principle of this procedure is to create a joint that will function mechanically correctly, consequently, the head of the femur must be shaped in such a way as to move freely within the mold and the acetabulum must be shaped so as to allow the mold to move freely within it.

The greatest possible respect for anatomical structures should be exercised in exposing the hip, in doing the reconstruction of the hip, as well as in following up the patient afterwards. This is not a procedure to be attempted by even an experienced surgeon unless he has tried it out in a cadaver or seen the procedure performed by a surgeon who has had considerable experience in hip joint surgery.

## Book Reviews

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**Management of the Cardiac Patient.** By William G. Leaman, Jr. Pp. 705, with 255 illustrations, 2 in color. Philadelphia, 1940, J. B. Lippincott Co. \$6.50.

This book covers a much more extensive field than a treatise devoted only to therapeutics of heart disease. In each chapter the author discusses briefly the etiology, pathology, pathologic physiology, symptomatology, and physical signs of the type of cardiac disorder under consideration. In addition, roentgen and electrocardiographic records are reproduced and adequately explained. The management of the cardiac patient is then considered in detail and the chapter concluded by adding illustrative case reports and a brief discussion. Obviously such an arrangement makes the book a most practical one and one which should be extremely useful to the general practitioner.

The book abounds with numerous descriptive drawings, illustrations, and excellent photographs, all of which help to simplify the subject matter and to correlate the pathology of different forms of heart disease with the clinical and laboratory findings, such as the x-rays and electrocardiographs. This feature, coupled with case-history method of presentation, makes the volume a real contribution to the busy physician who cannot devote considerable time to the study of voluminous treatises covering the various aspects of heart disease.

Included in the volume are chapters on cardiac problems in surgical practice, the heart in pregnancy, physiotherapy in the treatment of heart disease, prescription of exercise, diet in heart disease, and social service in the treatment of heart disease, all of which are extremely important in the successful management of cardiac disorders, and which have not received adequate attention in other textbooks.

The author's style is simple, the subject matter reads smoothly and is easily understandable. The author's opinions are characterized by sound judgment. This book should find a worthwhile place with the other standard treatises on heart disease that are now available. It is highly recommended to the student and internist as well as to the general practitioner.

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**Applied Orthodontics.** By James David McCoy, M.S., D.D.S., F.A.C.D. Ed. 5. Pp. 333, with 227 engravings and 1 plate. Philadelphia, 1941, Lea and Febiger. \$4.50.

The information contained in McCoy's fifth edition (revised) is well organized and stated in terms easily understood. It is a text applicable to undergraduate teaching especially since the author does not emphasize any particular technique to the exclusion of others. The illustrations are consistently good and there are many of them. Due recognition has been given to value and importance of visual education.

The sequence in which the material is present is logical and creates interest in what is to follow.

The text contains a large share of the late developments in research and technique. The differences found in this revision from the former editions are mostly minor additions and a somewhat better arrangement of material.

**The Extra-Ocular Muscles. A Clinical Study of Normal and Abnormal Ocular Motility.** By Luther C. Peter, M.D. Ed. 3. Pp. 368, with 147 illustrations and 5 color plates. Philadelphia, 1941, Lea and Febiger. \$4.50.

The book is designed primarily for the student, and Peter has presented, as in his other editions, a clear, concise approach to this difficult subject.

As a whole, there has been little revision of the material. The main changes consist of a more complete presentation of the orthoptic procedures. In revising this chapter he has not only added more recent views, but has added material which will prove very valuable to the beginner in orthoptic work.

In the chapter on nystagmus considerable new material has been added and the entire chapter is revised. This was written in collaboration with Dr. Joseph C. Yaskin, Professor of Neurology in the Graduate School of Medicine, University of Pennsylvania. Although the chapter on surgery is fundamentally the same, he has increased its value by adding to it his work on muscle resection.

When one remembers how few recent books there are on this subject in the English language and how few are designed primarily for the student, the value of this book is more appreciated.

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**Spermatozoa and Sterility, A Clinical Manual.** By Abner I. Weisman. Pp. 314, with 77 illustrations. New York, 1941, Paul B. Hoeber, Inc. \$5.50.

As the author states, this monograph is addressed not only to the gynecologist and the urologist but also to the general practitioner who would like to diagnose and treat his own cases of sterility.

The descriptions of the normal and pathologic anatomy and physiology of spermatozoa are excellent. The techniques for the diagnosis of sterility are given in detail. One may be disappointed, however, that so little that is specific or new is known about the treatment of sterility. One of the unsolved problems that still baffles the endocrinologist is the sterile matings between apparently fertile individuals.

An extensive bibliography and workable index are appended. This book is the best summary of our knowledge concerning spermatozoa and sterility written to date.

# SURGERY

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## Original Communications

### THE LOCATION OF THE LATERAL SPINOTHALAMIC TRACT IN THE BRAIN STEM OF MAN

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THE PRECISE location of the lateral spinothalamic tract is of special importance since its transection has become a recognized neurosurgical procedure for intractable pain. Only a few studies on this tract have been made on Marchi material. The superiority of the Marchi technique in defining the exact position of fibers that are scattered or mixed with others is well recognized. The latest report on this subject is by Walker,<sup>1</sup> who reviews the literature admirably and describes the general course of these fibers as seen primarily in a case of left chordotomy at the upper thoracic level with death eighteen days later. He furnishes further proof of the termination of the lateral spinothalamic tract in the posterolateral ventral nucleus of the thalamus.

While chordotomy is common enough, death within a few weeks after the operation under circumstances that permit the application of the Marchi technique is sufficiently rare to warrant further study of this type of material. Dogliotti<sup>2</sup> has successfully interrupted these fibers at the upper border of the pons. Although it would appear from his report that section of the lateral spinothalamic tract at this high level may be somewhat hazardous, and although it is also recognized that the indication is rare for severing of the fasciculus in the brain stem (in preference to a high cervical chordotomy combined with rhizotomy of the posterior roots of the upper cervical nerves), still the occasion may arise when such operative intervention would be seriously considered. To minimize the risk involved in operating at such high levels, the detailed topography of the fibers involved should be thoroughly appreciated at various points along the brain stem. We have, therefore, car-

ried through the Swank-Davenport<sup>3</sup> chlorate-osmic-formalin technique blocks of tissue from every segment of the spinal cord and a complete series of blocks from the lower portion of the medulla oblongata well into the thalamus. The Swank-Davenport method blackens the fat droplets resulting from degeneration of the myelin sheath with less tendency to produce disturbing artifacts than with the conventional Marchi procedure. It also gives evidence of degeneration earlier than can be recognized by the usual Marchi technique (Swank<sup>4</sup>). Its utilization in neuropathology is strongly recommended.

#### MATERIAL AND METHOD

The tissue was obtained from a man 54 years of age who succumbed nineteen days after right chordotomy done in the fourth to fifth thoracic segment for the relief of pain due to a metastatic squamous-cell carcinoma invading the left lumbosacral nerve plexus. Fifty-two days before death (thirty-three days prior to the chordotomy) 1 c.c. of 95 per cent alcohol had been injected through the second lumbar interspace into the subarachnoid space, according to the method of Dogliotti,<sup>5</sup> with the patient lying on the right side. The relief from pain was so incomplete that anterolateral chordotomy was later performed by a dorsolateral exposure and a certain amount of rotation of the cord. After the chordotomy the loss of pain and temperature sensibility extended up to the sixth thoracic dermatome on the left side. Subjectively he was entirely relieved of pain.

The brain and spinal cord were removed eight and one-half hours after death. The brain was perfused through the arteries with 3,000 c.c. of a 5 per cent aqueous solution of magnesium sulfate containing 2.5 per cent potassium dichromate and left overnight in this reagent. After further fixation for a day in 10 per cent formalin, transverse blocks nearly 1 cm. thick were made of the brain stem and kept two days in 10 per cent formalin. The spinal cord was cut into its thirty-one segments (leaving a little pia on one side to act as a hinge and to keep the segments in proper sequence) and kept overnight in a liter of above magnesium-potassium sulfate and then two days in 10 per cent formalin. By coiling the spinal cord in a large round dish so that the cuts gapped, the fixer had intimate contact with the cut surfaces of all the blocks.

From each segment of the spinal cord 3 mm.-thick blocks next to the cut surface were taken and the entire brain stem cut into blocks of about this thickness. Blocks through the upper third of the midbrain and thalamus were made oblique, as shown in Fig. 21, in order to facilitate the following of the fibers as they scatter out near their termination.

These thin blocks (thirty from the spinal cord and twenty-five from the brain stem) were strung on a thread in easily identifiable groups



(with enough slack between blocks to permit them to lie flat) and kept ten days in twenty times their volume of an aqueous solution containing 0.6 per cent potassium chlorate, 0.2 per cent osmic acid, 1 per cent acetic acid, and 12 per cent formalin. After being washed in running water for twenty-four hours, the blocks were transferred directly to dioxan for three days (the solution changed daily) and infiltrated and embedded in 50° C. paraffin in flat-bottomed tins as previously described (Rasmussen<sup>6</sup>). Under proper temperature these soft paraffin blocks cut well at 50 $\mu$  and may be mounted on slides, without albumin fixative, by dissolving away the paraffin by means of xylol applied with a medicine dropper and allowing the excess xylol to evaporate until sections are flat but have not changed color. When drying has gone too far, the sections take on a lighter hue. Since the blackened fat retains its sharp contrast better without cover glass, sections may be covered with clarite (a substitute for balsam), which on drying forms a hard protective covering. Most of the well-impregnated sections were covered with clarite and cover glass. In general the amount of osmic acid was insufficient to penetrate completely the blocks so that only sections near the cut surfaces were reliable.

The substitution of dioxan and paraffin embedding for the usual alcoholic dehydration and celloidin embedding decreases the time element considerably.

Due to the difficulty in adequately showing the detailed location of the degeneration by photomicrographs, instructive levels were projected at a known magnification (varying from six to eight times the diameter) and the visible degeneration inserted. With the original slide under the microscope the finer distribution of the degenerated fibers was carefully inserted under a higher magnification. Every effort has been made to show faithfully the relative density of the blackened fat droplets. This procedure has the advantage of a clear background, free from disturbing artifacts.

#### RESULTS

Sections below the level of the incision show consistently some scattered degeneration in the ventral half of the right lateral funiculus, which diminishes in amount and shifts somewhat dorsally in lower levels. This is illustrated in Figs. 1 and 2. (In these and all subsequent cross sections the right side of the patient is on the left-hand side of the sketch.) This evidently represents descending reticulospinal fibers with possibly a few rubrospinal fibers, mostly dorsally. In the left dorsal funiculus, commencing with the lower lumbar segment and increasing in amount to the upper lumbar level, is considerable degeneration which represents the dorsal root fibers that were alcoholized one month before chordotomy was performed. From the degeneration found in different levels from the lower thoracic to the lower sacral region, it is clear that effect of the alcohol was confined to the region of the left

ried through the Swank-Davenport<sup>3</sup> chlorate-osmic-formalin technique blocks of tissue from every segment of the spinal cord and a complete series of blocks from the lower portion of the medulla oblongata well into the thalamus. The Swank-Davenport method blackens the fat droplets resulting from degeneration of the myelin sheath with less tendency to produce disturbing artifacts than with the conventional Marchi procedure. It also gives evidence of degeneration earlier than can be recognized by the usual Marchi technique (Swank<sup>4</sup>). Its utilization in neuropathology is strongly recommended.

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shown in Fig. 3, which is just above the incision. Immediately above the lesion the area transected is well delimited by the degeneration and extends over most of the ventral half of the lateral funiculus. The superficial degeneration extending dorsally from the main area may be due to traumatization of the surface of the cord just dorsal to the point of entrance of the knife. This is in the region of the attachment of the dentate ligament, traction on which was used to rotate the cord.

At higher levels (Figs. 5 and 6) there is confirmation of the conclusions arrived at by Hyndman and van Epps<sup>7</sup> with reference to the extent of the lateral spinothalamic tract. These ascending fibers cover a much larger cross section area and spread out more ventromedially than is shown in standard texts.

The extent of the involvement of the dorsal spinocerebellar tract of Flechsig is best defined in Figs. 7 to 12, which show them finally entering the restiform body. Their course within the cerebellum, curving dorsally, medially, and downward, and fanning out in the vermis, is readily seen in the material but not reproduced.

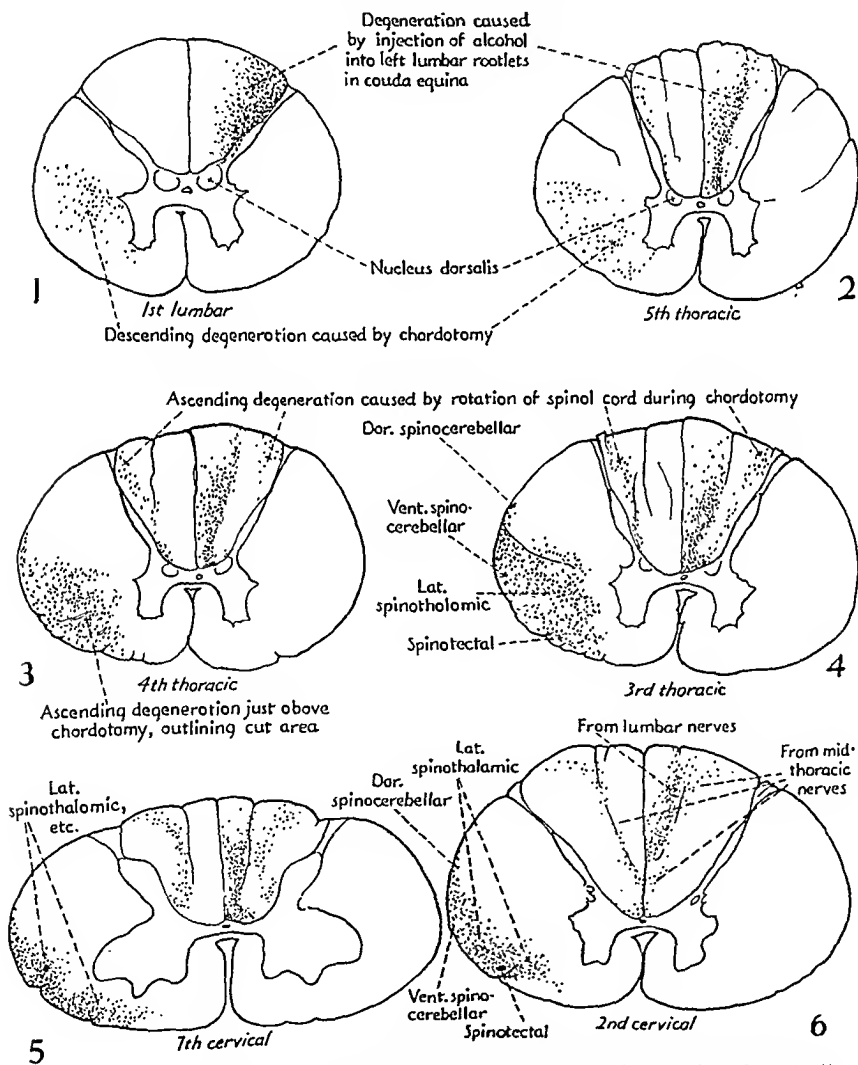
The rest of the degeneration in the lateral column consists of the ventral spinocerebellar tract of Gowers (most lateral and superficial), the small spinotectal tract (most ventrolateral), and the lateral spinothalamic tract, which constitutes the more medial and greater bulk of the degeneration. These tracts are shown in Figs. 7 to 11 in their typical position through the medulla oblongata. Near the lower pole of the inferior olive (Fig. 10) these fibers extend medially to about one-third of the distance to the midsagittal plane or about 4 mm. in the actual brain stem. Higher in the medulla (Fig. 11) they extend somewhat more medially, to a depth that makes their complete surgical interruption in this region hazardous, although the approach would be the same as for section of the descending root of the trigeminal nerve, as practiced by Sjöqvist<sup>8</sup> and others.<sup>9</sup>

Through the pons the three tracts are deeply buried. In Fig. 12 they are seen between the superior olivary nucleus and the distal part of the intrapontine portion of the facial nerve. In the upper pons they again become superficial as is illustrated in Fig. 13. Here is where Dogliotti interrupted the pain circuit.

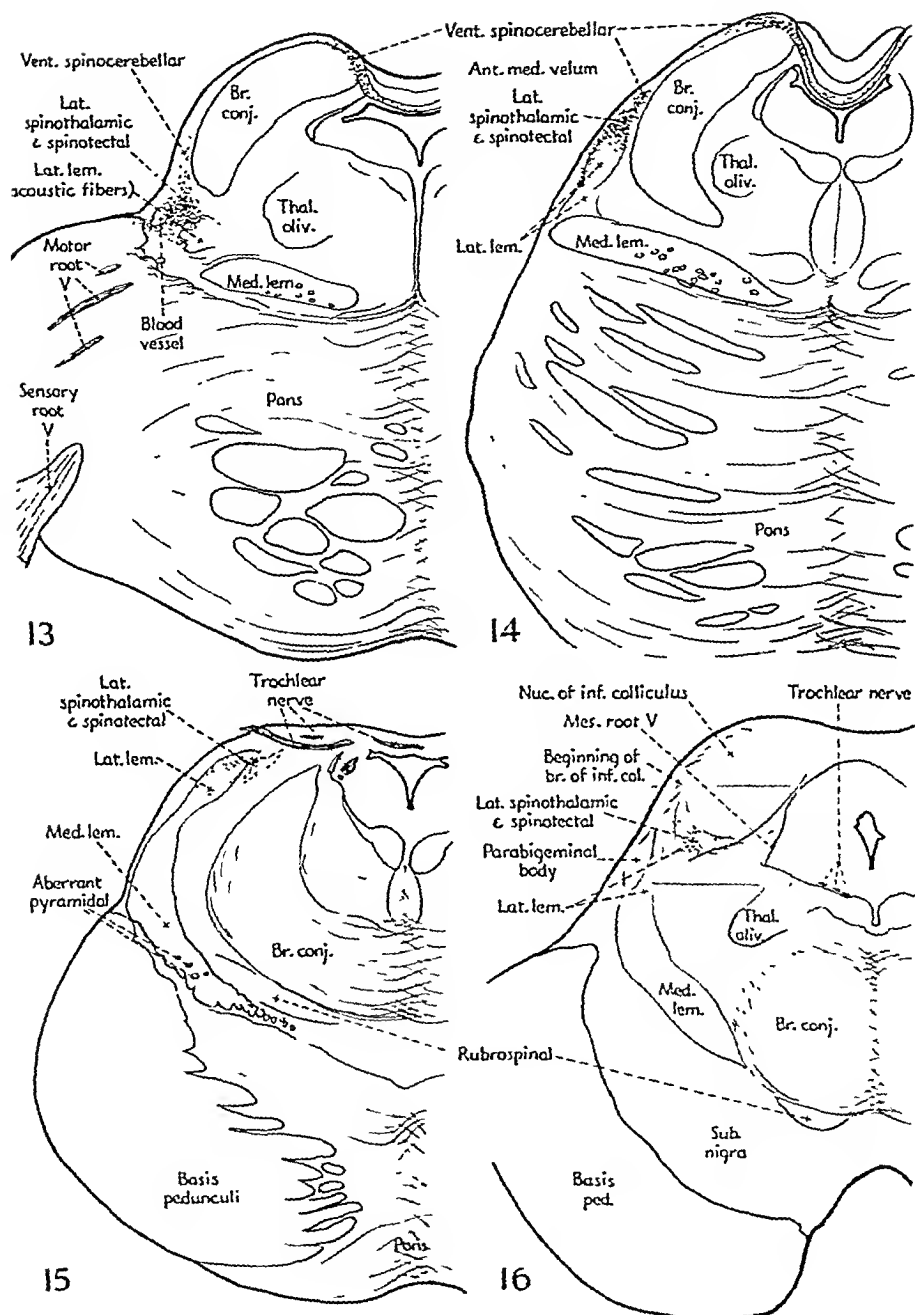
It would appear that a slightly higher level, as in Fig. 14 (compare with Fig. 21), i.e., not over 5 mm. below the fourth cranial nerve, would be a better place to cut the tract. Here (in the widest part of the trigonum lemnisci) it is spread out in a very superficial sheet less than 2 mm. in thickness, so that a shallow incision not over 2 mm. deep and about 5 mm. transversely across the central portion of the trigonum lemnisci should suffice. Some damage to the underlying superior cerebellar peduncle (brachium conjunctivum) would not be serious. Neither would ventral prolongation of the incision be of any consequence, because this would merely get more of the central acoustic

lumbar roots. This degeneration, as it shifts its relative position at higher levels, marks rather sharply the lumbar component of the dorsal column. Its association with nucleus gracilis is shown in Figs. 8 and 9.

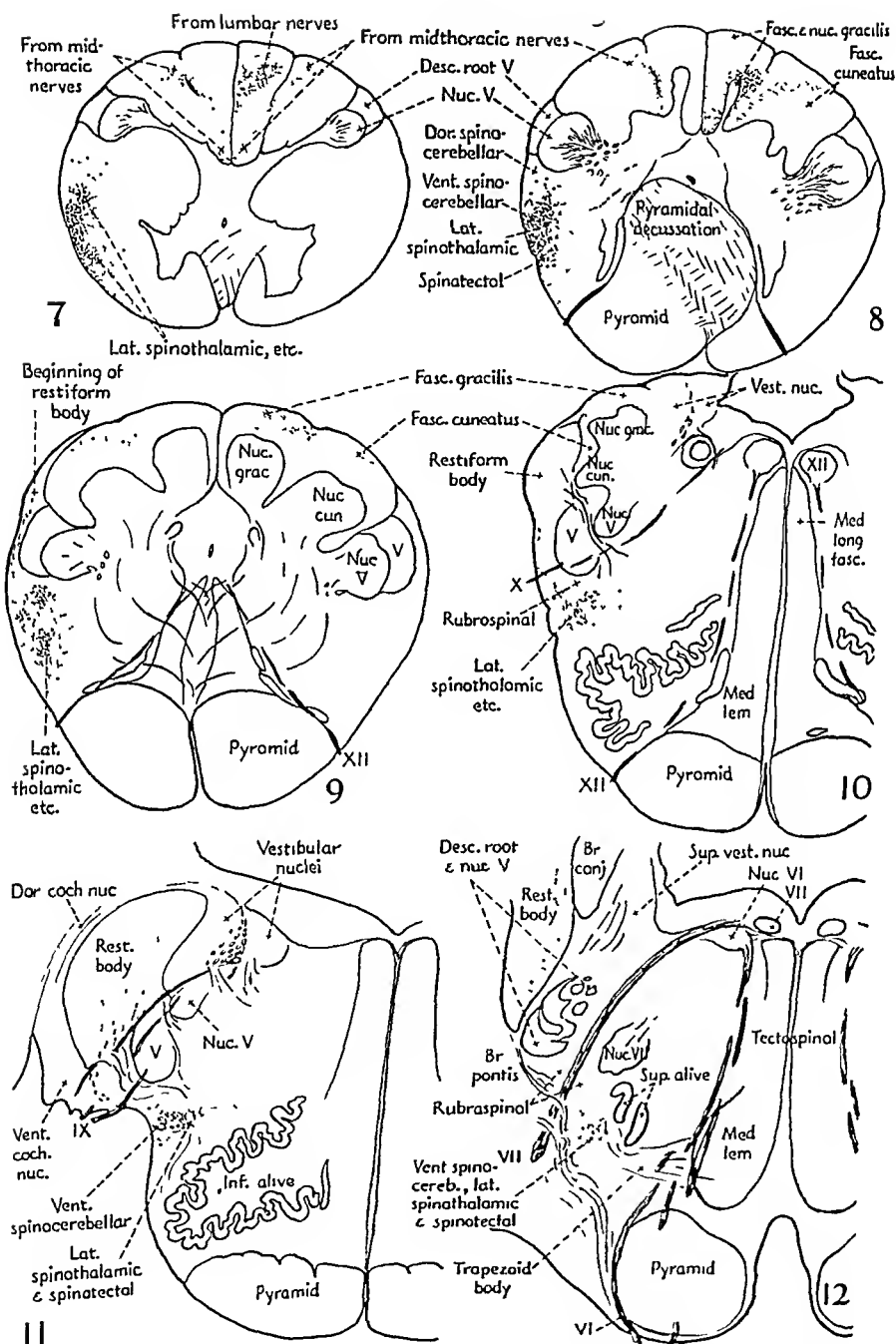
In the region of the operative site, additional degeneration appears bilaterally in the lateral portion of the dorsal funiculi. This is somewhat more extensive on the right side than on the left. It is evidently due to operative exposure and traumatization of neighboring dorsal roots during rotation of spinal cord, in spite of exercising care during traction on the dentate ligament. This degeneration from trauma is



Figs. 1-6.—Various levels of spinal cord showing degeneration in dorsal funiculi resulting from injection of alcohol into lumbar roots and trauma of dorsal roots incident to exposure and rotation of spinal cord during chordotomy in fourth or fifth thoracic segment. Ascending tracts interrupted by chordotomy are shown in Fig. 1 and higher levels. (X4.)



Figs. 13-16.—Upper pons and lower midbrain showing particularly superficial position of lateral spinothalamic tract ( $\times 3$ ).



Figs. 7-12.—Various levels of medulla oblongata showing degeneration as in preceding ( $\times 3\frac{1}{2}$ ).

fibers of the lateral lemniscus, and each ear is bilaterally represented in this pathway. Dorsal prolongation would only involve the already degenerated ventral spinocerebellar tract and the dorsal portion of the brachium conjunctivum.

At the level of emergence of the trochlear nerve (Fig. 15) the dorsal spinocerebellar tract is no longer present (having turned dorsally and downward into the anterior medullary velum), and the remaining degeneration (now representing only the lateral spinothalamic and spinotectal tracts) is more dorsal in position with reference to the trigonum lemnisci. Here the brachium conjunctivum is less likely to be encountered since it is shifting ventrally. A stab wound 3 mm. deep, commencing at the attachment of the fourth nerve and extending ventrally 3 or 4 mm., should be ample to interrupt pain completely.

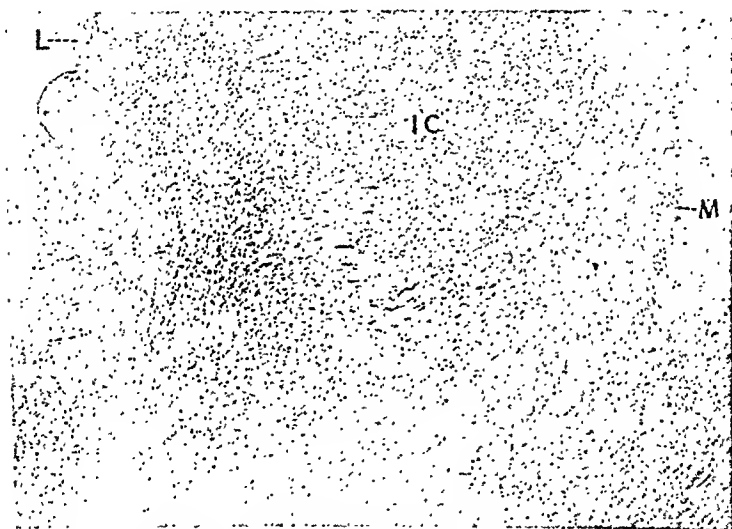
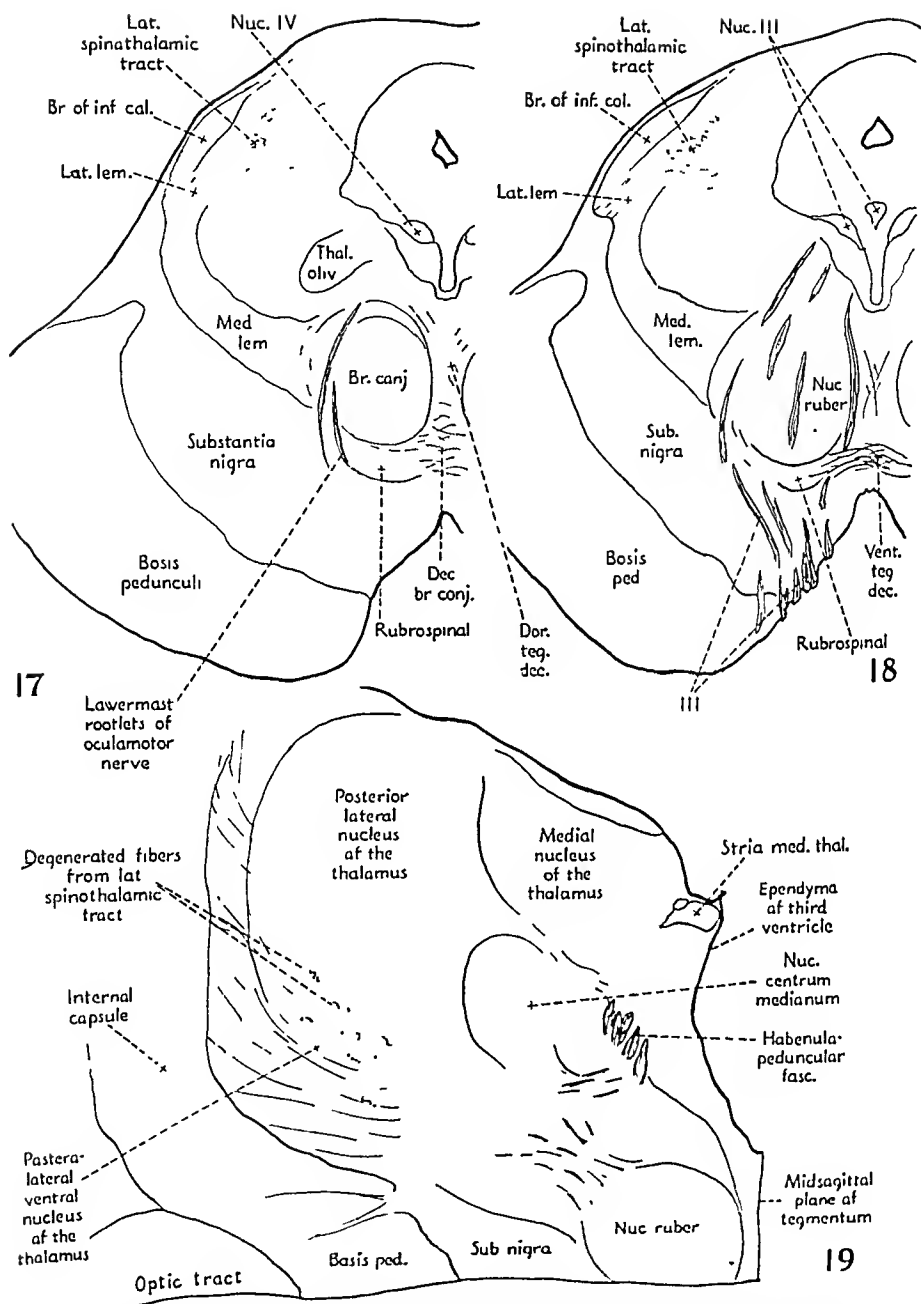


Fig. 20.—Photomicrograph of region squared in Fig. 16. Shows the close relation of the lateral spinothalamic tract to the nucleus of inferior colliculus. *L*, Lateral surface of midbrain; *M*, mesencephalic root of trigeminal nerve; *IC*, nucleus of inferior colliculus. ( $\times 15$ .)

A certain allowance must be made for fibers from the upper regions of the spinal cord since these were not cut in this case. The total bulk of pain fibers from the entire spinal cord is therefore greater than shown here. These additional fibers would enlarge the tract somewhat, especially medially, in comparison with the area of degeneration here shown.

While the statement is made that the lateral spinothalamic tract passes through the inferior colliculus (posterior corpus quadrigeminum), it was not appreciated that they were so intimately mixed with the heavy triangular myelinated area in contact with the ventral border of the nucleus of the inferior colliculus. This region has generally been assumed to be largely auditory fibers which were destined to terminate



Figs. 17-18.—Intercollicular region of midbrain showing lateral spinothalamic tract more deeply situated. Note spinothalamic fibers ( $\times 5$ ).  
 Fig. 19.—Oblique section (see Fig. 21) through posterior region of thalamus showing few fibers of lateral spinothalamic tract ( $\times 5$ ).



supratentorial in position and topographically easily identifiable. The nucleus of the inferior colliculus may be ignored as far as consequences following its partial destruction are concerned.

Above the inferior colliculus (Figs. 17 and 18) where the brachium of the inferior colliculus forms a prominent ridge coursing upward and slightly ventrally toward the medial geniculate body, the spinothalamic fibers are well beneath (medial to) this brachium, as noted by others.

The number of degenerated fibers that could be positively identified in the oblique sections through the lower part of the thalamus was disappointingly few. As shown in Fig. 19, only an occasional fiber could be clearly recognized and this was in the posterolateral portion of the ventral nucleus of the thalamus as maintained, especially by Walker.

The ascending degeneration, consisting mostly of the lateral spinothalamic tract, has been projected on to a side view of the brain stem (Fig. 21) in order to give a more general view of its superficial projection. The heavy transverse planes numbered from 7 to 19 represent the position of the correspondingly numbered figures. Since section of the descending (spinal) root of the trigeminal nerve is being done as a substitute for partial extrapontine section of the sensory root of this nerve, the superficial projection of this root and other portions of the fifth cranial nerve have been included in the same sketch. Careful attention has been given to the position of the descending root in the region of the lower half of the inferior olive where these fibers are most often interrupted surgically, the projection being based on about 100 gross dissections.

#### SUMMARY

A description is given of the degeneration resulting from preliminary injection of alcohol into the left lumbar roots of the spinal nerves followed thirty-three days later by right chordotomy at the fourth to fifth thoracic region with death nineteen days after the chordotomy.

The usual shifting in position (in ascending levels) of the lumbar component of the dorsal funiculus (due to injection of alcohol) is well demonstrated as is also that of the fourth to fifth thoracic component (due to trauma incident to rotation of the cord).

The area of degeneration resulting from the cutting of the spinothalamic and associated tracts is larger than usually shown and thus confirms Hyndman and van Epps.

The position of the lateral spinothalamic tract through the brain stem is shown in cross sections as well as in surface projection. These fibers are most superficial in the region of the trigonum lemnisci just below the trochlear nerve, where they could readily be interrupted for relief of pain without serious consequences from direct injury to adjacent structures.

within the nucleus of the inferior colliculus. But the sections through this region (Fig. 16) are sharply stained and free from artifacts so that interpretation is attended with great certainty. A sufficiently high power photomicrograph of the region blocked out in Fig. 16 is shown in Fig. 20. Spinothalamic fibers are seen straying medially and dorsally into the region between the nucleus of the inferior colliculus and mesencephalic root of the trigeminal nerve. This is true of all of the section from slightly below this level well up into the superior colliculus. A 3 mm. stab wound extending 5 or 6 mm. into the ventral part of the inferior colliculus would appear feasible. This location is distinctly

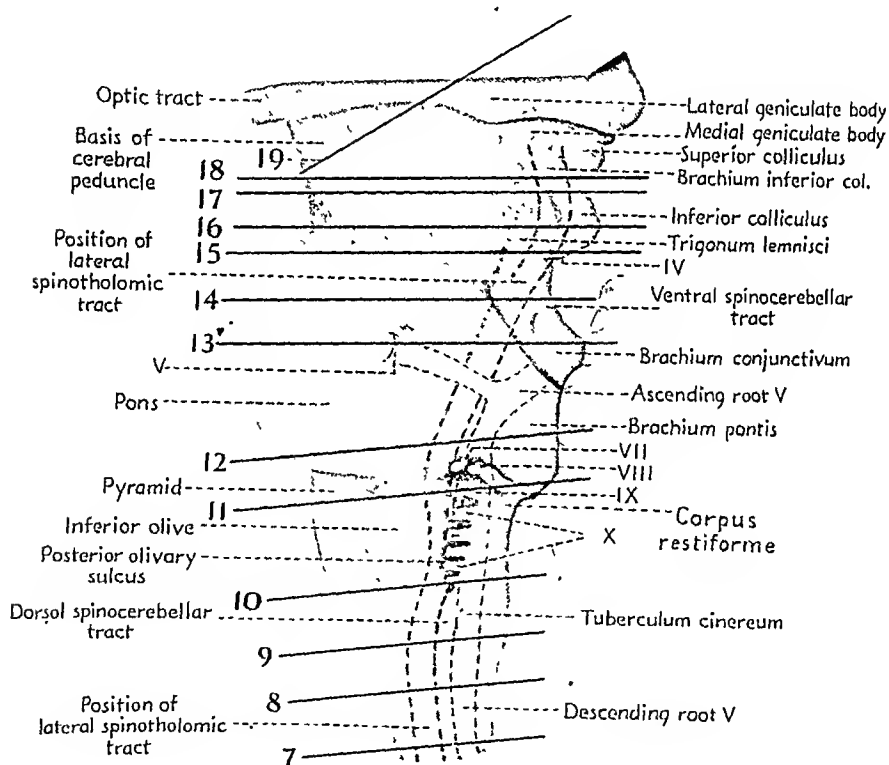


Fig. 21.—Drawing of lateral view of adult human brain stem with salient topographic features and projection of lateral spinothalamic tract and trigeminal nerve onto the surface. Numbers 7 to 19 indicate positions of cross sections shown in preceding figures with corresponding numbers. As far as location within the brain stem is concerned, the lateral spinothalamic tract is most easily accessible just below Level 15. This would appear to be a better location for interrupting it than at Level 11, where the tract has been severed. Just below Level 15 a shallow incision only 2 to 3 mm. deep and 5 to 6 mm. long transversely across the central portion of trigonum lemnisci should include the entire tract.

Tractotomy for relief of facial pain is being done at Level 16 of this figure. The descending root V is here covered by only a thin sheet of fibers belonging to the dorsal spinothalamic tract. Dorsally the restiform body may slightly overlap. The lower rootlets of the vagus nerve emerge just ventral to the descending root of the trigeminal nerve. It is more probable that vagus rootlets are involved when tractotomy is followed by recurrent palsy than that the incision was too deep and damaged nucleus ambiguus, as assumed by some. ( $\times 1\frac{1}{2}$ )

# THE REPAIR OF A CRANIAL DEFECT WITH A VITALLIUM PLATE

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THE repair of cranial defects is a problem to the surgeon. Grant and Noreross<sup>1</sup> in 1939 made an exhaustive study of the literature and found more than 1,300 cases of cranioplasty described. It is unnecessary to duplicate their report, but for a complete review of cranioplastic procedures their paper should be consulted. However, some of the pertinent facts on cranioplasty bear repetition.

## HISTORICAL

Macewen in 1873 reimplanted bone into cranial defects. The bone was removed from the patient's skull, sterilized with antiseptics, and then replaced into the defect. Von Hinterstoisser<sup>2</sup> in 1891 was the first to describe the use of a nonosseous substance in the repair of cranial defect when he resorted to a celluloid plate. In 1893 Booth and Curtis<sup>3</sup> employed an aluminum plate to cover a cranial defect. Two years later Gerster<sup>4</sup> described the application of a gold plate. Sieard and Dambrin<sup>5</sup> in 1917 reported a case in which cadaver skull bone was used to repair a defect of the cranium. During the past forty years many surgeons have used both split rib grafts and cartilage to repair cranial defects. Fair success has been encountered with both rib and cartilage grafts, but most authors claim that cartilage has a little too much "give" and because of this fact it does not offer sufficiently firm support.

## VARIOUS OPERATIVE TECHNIQUES

In 1890 Müller<sup>6</sup> described a skull flap technique for the repair of a cranial defect. This procedure consisted in the elevation of a skin flap over the defect and then removal of an area of outer table from the adjacent bone, sliding it over to cover the defect. In the same year König<sup>7</sup> improved upon Müller's operation when he developed a twin flap technique. One flap consisted of skin and what remained of the perieranium over the defect, and the second flap contained skin, perieranium, and outer table. The bases of these two flaps were opposite but not directly in line with each other. The flap containing the outer table was swung over to cover the defect, while the other flap was used to cover the bared inner table. Small exposed areas produced by this crossing of flaps were covered with Thiersch grafts.

One is apparently justified in the assumption that no entirely satisfactory method has been developed for the repair of large cranial defects.

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## INDICATIONS AND CONTRAINDICATIONS

Most authors agree upon the indications and contraindications for cranioplasty which have been listed by Grant and Norcross as follows:

*Indications:*

1. Severe headache
2. Syndrome of the trephined (dizziness, apprehension and feeling of insecurity, undue fatigability, mental depression, and intolerance to vibration)
3. Epilepsy, if the attack is related to the injury
4. Danger of trauma at the site of defect
5. Unightly defect
6. Painful defect or undue pulsation

*Contraindications:*

1. Presence of a foreign body
2. Infection of the skin, dura, or brain tissue
3. Increased intracranial pressure
4. Abnormal spinal fluid findings

## TYPES OF CRANIOPLASTIC MATERIAL

An ideal cranioplastic material should be: (1) nonirritating, both electrically and chemically; (2) strong and inelastic; (3) light weight; (4) nonabsorbable; and (5) malleable.

None of the materials used for cranioplasty have been entirely satisfactory. Either cadaver or fresh human bone may absorb or fail to unite solidly. If infection occurs, the bone graft may slough out.

Vitallium, an alloy of chrome, cobalt, and molybdenum, was developed for the dental profession in 1929 in a search for an inactive metal. In 1936 Venable and Stuck reported their experiences with vitallium in bone surgery. They found it to be absolutely inactive when it is in contact with tissue. No changes could be detected either in the tissue or in the metal itself. It has been used in bone surgery for the past four years and has proved most satisfactory. Vitallium is not malleable, but this is chiefly a manufacturing disadvantage and not a surgical one. Malleability of the metal used, however, is desirable at times in order that a plate be molded to fit a part, but this is of minor importance among the requirements for a suitable cranioplastic substance.

## REPORT OF A CASE

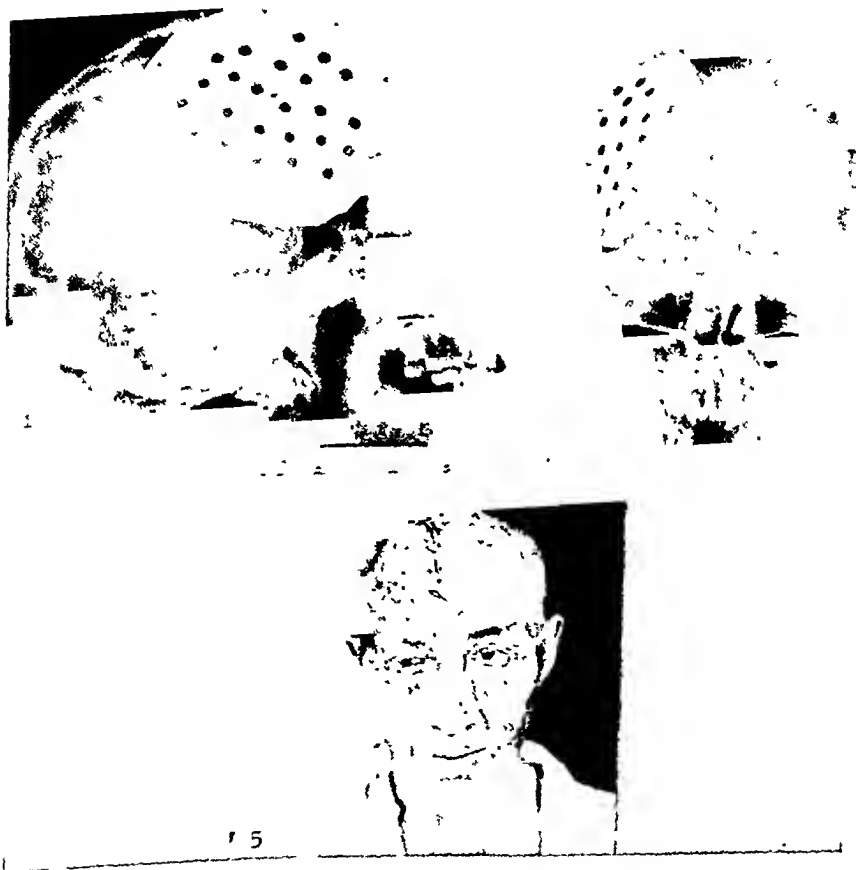
The employment of vitallium by the orthopedic staff prompted us to investigate the possibility of fashioning a plate from this alloy to cover a cranial defect in the following case:

T. E. (U.H. 690902), a 61-year-old white male, was referred to the University of Minnesota Hospital Clinics for the diagnosis and treatment of a tumor mass involving the right side of the skull. The patient gave a history that the mass first appeared in March, 1939. The patient's local physician explored the tumor and removed a piece for biopsy, following which the patient received a series of deep x-ray treatments in July, 1939. The tumor continued to enlarge and in January, 1940, the patient was referred to the University of Minnesota Hospital for further

care. His only complaints were a mass on the right side of the head and an occasional headache. Examination was negative except for the presence of a firm, non-tender, fixed tumor mass about 10 cm. in diameter involving the cranium over the right frontoparietal region. Roentgenograms of the skull showed changes suggestive of a meningioma. On Feb. 7, 1940, through a right transfrontal incision a meningioma was excised, removing the involved bone and meningioma en masse. This left



a cranial defect 11 cm. in diameter and nearly round. Following an uneventful convalescence, the patient was dismissed on Feb. 16, 1940. Three months later the patient returned to the Out-Patient Clinic for a checkup. At that time he complained of a feeling of insecurity as he was afraid of suffering an injury at the site of the skull defect. Also great changes in temperature, such as the application of hot or cold water to the defect, were quite unpleasant. Examination at that time was negative except for the pulsating defect. The patient desired that something be done to cover the area of excised bone. As the defect was so large, it would have been nearly impossible to carry out a Müller-König procedure; therefore, this case appeared to be the type suitable for the application of a vitallium plate.



Figs. 4 and 5.—Fig. 4, Roentgenograms to show vitallium plate in place; Fig. 5, two weeks after insertion of plate.

*Construction of a Model.*—A plaster mold was made of the right side of the skull and upper part of the face. This mold acted as the negative model. With the help of the dental department, a positive model was made and in this way an exact duplication of the cranial defect was obtained. Wax was poured into the defect and molded to conform with the surrounding contour. The wax model thus became an exact replica of the excised bone. From the positive plaster mold and wax model the plate was cast.

Fixation of the plate to the skull is a problem for each individual case. One might add "ears" to the edge of the plate. Through a hole in the center of each ear,



the plate could be fixed to the skull by screws. However, after making several such models, fixation by this method did not seem adequate; also, if it were necessary to remove bone at the time of application of the plate, the plate might fail to cover the enlarged defect. With this thought in mind, other plates were devised. The plate which seemed to be most practical was one which had a 1.5 cm. edge added beyond the edge of the defect, about two-thirds of the way around its circumference on its superior, anterior, and posterior margins. This added width allowed the plate to rest against bone over this part of the circumference. Holes were placed in the extended portion of the plate 0.5 cm. from the edge and 4 cm. apart. Larger perforations were also placed throughout the plate in order to allow the development of adhesions and blood supply between the scalp and underlying tissue.

*Operative Procedure.*—The patient was readmitted to the hospital for application of the vitallium plate on June 27, 1940. The skin and scalp flap was re-elevated, exposing the operative defect. After removal of a small amount of bone, the plate covered the defect quite satisfactorily. The overlapping rim contacted the surrounding bone snugly. The overlap was sufficient to allow fixation of the plate to the skull either by screws or wire. Stainless steel wire was used in this case as the vitallium screws which had been made to order were too short. Screws for fixation should be pointed similar to the wood type of screw and they should be  $\frac{3}{16}$  to  $\frac{1}{4}$  inch long. Because the prepared screws were not suitable, two small drill holes 0.5 cm. apart were placed in the skull directly under a hole in the plate. One end of the wire was passed through one hole in the skull and then back out through the second hole and on through the hole in the plate. The other end of the wire was brought around the edge of the plate and the ends were twisted. Three sets of holes and wires gave adequate fixation. The skin flap was reapproximated without difficulty. The convalescence was smooth except for an accumulation of fluid between the skin flap and plate which necessitated aspiration five or six times. Postoperative roentgenograms of the skull showed the plate to cover the defect adequately.

Since the insertion of the plate, the patient has experienced much relief through a feeling of security against injury. Sudden changes in temperature no longer are unpleasant to him. The cosmetic result is very satisfactory.

#### CONCLUSIONS

Vitallium, an alloy of chrome, cobalt, and molybdenum, is the most inactive and practical alloy yet offered to the surgeon.

A vitallium plate offers the surgeon an almost ideal material for closure of cranial defects caused by the loss of bone.

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## THE GLYCOGEN CONTENT OF THE HUMAN LIVER\*

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IN RECENT years much attention has been focused on the value for surgical patients of a diet high in carbohydrate or protein, or high in both, particularly in relation to the level of liver glycogen in instances of hepatic disease. Unfortunately, little is known concerning the effect of diet, anesthesia, and liver pathology upon the glycogen levels of the living human liver, except by inference, as the greater part of our knowledge has been obtained either from analyses carried out on human livers at the time of autopsy or from experimental work on animals.

The purposes of this paper are: (1) briefly to review a part of the literature relative to glycogen levels of the human liver at the time of autopsy, and (2) to present and discuss the glycogen values in the human liver obtained from biopsy specimens during surgical operations.

The great French physiologist, Claude Bernard, was the first to find in animal livers a substance similar in composition to starch in the vegetable kingdom. He named it glycogen. Although follow-up studies were mainly carried out by other investigators, Bernard did show that there was a rapid postmortal change of liver glycogen into glucose. Yet, in spite of this timely warning, many subsequent workers have entirely disregarded the fact and directly determined liver glycogen twenty-four to forty-eight hours after death and have drawn conclusions from these findings in regard to the glycogen values present during life. The most unusual claim found in this connection was that of Krukow,<sup>1</sup> who stated that at room temperature animal and human livers require a high state of decomposition and as long as sixty-eight days to change the greater part of the glycogen into glucose.

Determinations of glycogen in the human liver at the time of autopsy have been carried out either by chemical or histologic methods, sometimes by both. Histologic determinations can at best only be semi-quantitative and will not be discussed here. Several references, however, will be included in the bibliography and particular attention is called to the great amount of medicolegal work by Meixner<sup>2</sup>,<sup>3</sup> relative to the level of glycogen and the cause of death. Chemical determinations of liver glycogen can arbitrarily be grouped according to the

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method employed. The first and direct method was based upon the extraction of glycogen from the liver by hot water and the subsequent weighing of the dried glycogen. Bernard used this method in part of his work. Külz, in 1876,<sup>4</sup> determined glycogen on a part of a diabetic liver twelve hours after death and estimated that there were 10 to 15 Gm. in the whole gland. In 1881<sup>5</sup> he reported 5.28 per cent in another case. Cramer, in 1888,<sup>6</sup> boiled the liver in strong potassium hydroxide, precipitated the glycogen with alcohol and weighed the glycogen. In the livers from 3 infants he found respectively 1, 1.2, and 2.15 per cent. Schönheimer, in 1929,<sup>7</sup> found 10.4 per cent in a case of von Gierke's disease, and as high as 15.3 per cent has been reported in this condition.<sup>8</sup> The values obtained by water extraction of glycogen of necessity must have been minimum values as one can seldom obtain the liver from cadavers until after several hours of delay and, furthermore, the extraction by hot water is long and tedious, as well as likely to be incomplete.

The second method was based upon the destruction of the liver tissue by hot potassium hydroxide. This treatment leaves glycogen intact so that it can be precipitated by alcohol, washed, dried, and weighed, or the glycogen can be subjected to acid hydrolysis yielding glucose which can be determined by (a) various oxidizing solutions or (b) the aldehyde color reaction. By the use of the first method, Rosenbaum<sup>9</sup> found in 19 infant livers no glycogen in 6, traces in 6, and from 0.23 to 3.27 per cent in the remainder. Geelmuyden<sup>10</sup> in 14 cases found values between 0.0 and 3.02 per cent. Sandmeyer<sup>11</sup> found 0.61 per cent and Helly<sup>12</sup> 0.45 per cent. Both cases died in diabetic coma. Among French investigators, Lacassagne and Martin<sup>13</sup> found on an average from 2 to 3 per cent in the liver of persons dying a violent death. Later<sup>14</sup> they claimed a variation between 2 and 4 per cent. Garnier<sup>15</sup> also reported 2 to 4 per cent.

The aldehyde reaction of Dische and Popper<sup>16</sup> was applied by Burghard<sup>17</sup> and by Burghard and Paffrath.<sup>18, 19</sup> In 100 livers they reported for healthy infants 2 to 3 per cent and 6 to 8 per cent for healthy adults. In disease much lower values were found; only about one-third were above 1 per cent with a total range between 0.2 and 5.45 per cent. These authors concluded that there was a definite and constant difference between total carbohydrate determined as glucose and the glycogen. This difference was set by them arbitrarily at 0.23 which, when subtracted from the total carbohydrate, indirectly would give glycogen present "at the time of death." This constant difference was not confirmed by Hertz,<sup>20</sup> who reported variations between 0.46 and 12.6 per cent in a series of 2 newborn infants and 7 fetuses.

By far the most work using the aldehyde method was by Popper and Wozasek who studied 177 human livers.<sup>21-24</sup> In a long article<sup>21</sup> they classified their findings according to the disease but, stated briefly, their

glycogen values were between 0.24 and 8.5 per cent. With a few exceptions, values were between 1.56 and 6.17 per cent in patients dying suddenly without previous disease; while in livers from patients dying after long-standing diseases the values ranged between 0.24 and 1.53 per cent. It should be pointed out, also, that there was a tendency towards lower values in hepatic diseases.

These figures for liver glycogen are levels found at the time of autopsy. They do not, therefore, represent actual values which one might expect to find in sick or healthy persons during life. It should be pointed out here that the values for liver glycogen found in our study were influenced by many factors and, also, do not necessarily represent those found in the normal living human liver. Some of our patients had morphine preoperatively and "morphine diabetes" has been known for more than sixty years. Frank and Förster<sup>25</sup> showed in rabbits a marked decrease in liver glycogen after morphine. The same effect upon blood sugar and liver glycogen has also been observed after the administration of certain anesthetics. Evans and his associates<sup>26</sup> found a 20 per cent decrease in the liver glycogen of rats killed after ten minutes of an ether anesthetic and a decrease of 50 per cent after one hour. Rhythmic changes in the level of liver glycogen were observed by Forsgren<sup>27, 28</sup> and confirmed by others.<sup>29-32</sup> There may even be more than one type of glycogen present in the liver<sup>33</sup> and it has been claimed that certain foods as well as specific sugars form a glycogen more stable than usual. Since our liver specimens were obtained by biopsy, it is important to know if liver glycogen is equally distributed throughout the liver. In the older literature there was disagreement in regard to this point, but more recent work<sup>34-36</sup> indicates that the content of the different lobes is sufficiently uniform that a specimen from one lobe is indicative of the whole. Experiments by us on the rat liver also favor this view.\* In addition there are the general state of nutrition of the patient and the degree and duration of liver damage as well as the effect of the hormones from the thyroid, pancreas, and adrenal glands. One factor, namely, the postmortal change of glycogen into glucose, did not influence the data to be presented. The importance of this factor is shown by the finding of 0.55 per cent and 0.05 per cent of liver glycogen, by the method later described, in 2 human autopsy livers without sign of liver damage obtained two and sixteen hours respectively after death.

#### PROCEDURE

The Good, Kramer, and Somogyi<sup>17</sup> modification of Pfluger's classical method was used for the glycogen determinations. The biopsy specimens were frozen immediately in carbon-dioxide snow and ether in the operating room. While still solidly frozen the specimens were ground very fine and transferred into weighed centrifuge tubes containing

\*Unpublished data.

potassium hydroxide, were quickly weighed and placed in a beaker of boiling water. After the specimen was in solution, the glycogen was precipitated and hydrolyzed and then the total reducing sugar was determined on aliquotes in duplicate according to the method of Shaffer and Somogyi.<sup>38</sup> The liver specimens, removed from the liver edge, weighed 0.5 to 1.5 Gm. Bleeding was very easily controlled by inserting a small piece of abdominal wall muscle into the liver wound and approximating the cut surfaces with silk sutures. No glucose was given parenterally during the operations. The general health of each patient was estimated as being good, fair, or poor. A small piece of the liver specimen was sent to the Department of Pathology for histologic examination and was graded normal or showing slight, moderate, or advanced damage. The time of the biopsy from the onset of the anesthetic was recorded as was also any supplementary glucose feeding within twelve hours prior to the operation. These and other pertinent data are given in Table I.

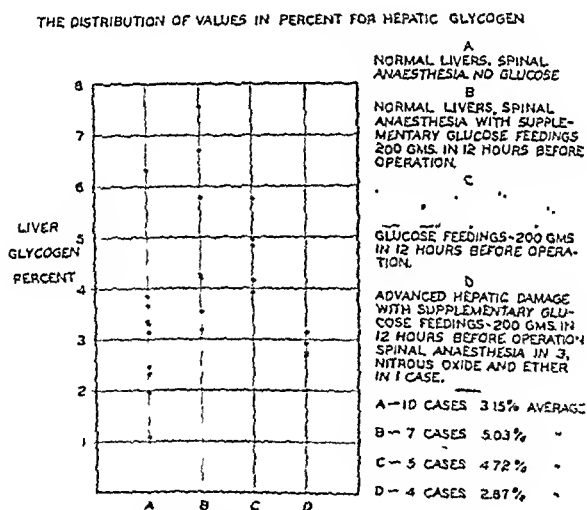


Fig. 1—Analysis of data, dividing the patients into groups according to the anesthetic, the liver pathology, and whether or not they received supplementary feedings of glucose in the twelve hours immediately preceding the operation.

## RESULTS

In the 33 cases studied and summarized in Table I, the average glycogen content was 3.96 per cent, the lowest value was 1.1 per cent, and the highest 7.56 per cent. Fig. 1 is an analysis of these data dividing the patients into groups according to the anesthetic, the liver pathology, and whether or not they received supplementary feedings of glucose in the twelve hours immediately preceding the operation. Except in those instances in which glucose was given, the patients did not receive food or fluid in the twelve hours before the operation. All cases

TABLE I

COLLECTED DATA ON 33 PATIENTS IN WHOM BIOPSIES OF THE LIVER WERE OBTAINED AND PERCENTAGE OF HEPATIC GLYCOGEN DETERMINED

PATIENT	AGE	SEX	AVERAGE WEIGHT (KG.)	PRESENT WEIGHT (KG.)	ESTIMATE OF GENERAL HEALTH	DIAGNOSIS	DURATION OF SYMPTOMS	LIVER HISTOLOGY	ANESTHESIA	TIME FROM ONSET FOR ANESTHESIA TO BIOPSY (MIN.)	SUPPLEMENTARY GLUCOSE FEEDINGS IN 12 HR. PREOPERATIVELY (GM.)	PER CENT LIVER GLYCOGEN	POST-OPERATIVE COURSE	GROUP
1	23	F	67	60	Fair	Cholecystitis	4.3 mo.	Normal	Spinal	45	0	1.10	Fair	A
2	27	F	68	51	Fair	Duodenal ulcer	24 mo.	Normal	Spinal	39	0	1.99	Fair	A
3	51	F	61	46	Poor	Duodenal obstruction	4 mo.	Normal	Spinal	35	0	2.32	Death after 4 days	A
4	58	F	84	85	Good	Cholecystitis	24 mo.	Normal	Spinal	42	0	2.48	Good	A
5	61	M	72	59	Fair	Gastric carcinoma	9 mo.	Normal	Spinal	38	0	3.12	Good	A
6	52	M	90	75	Good	Cholecystitis	36 mo.	Normal	Spinal	60	0	3.31	Good	A
7	30	F	53	53	Good	Cholecystitis	24 mo.	Normal	Spinal	45	0	3.24	Good	A
8	50	F	54	54	Good	Cholecystitis	6 mo.	Normal	Spinal	40	0	3.68	Good	A
9	21	F	77	77	Good	Cholecystitis	12 mo.	Normal	Spinal	50	0	3.85	Good	A
10	50	F	68	64	Good	Cholecystitis	12 mo.	Normal	Spinal	39	0	6.31	Good	A
11	53	M	68	64	Good	Cholecystitis	10 yr.	Normal	Spinal	25	200	3.19	Fair	B
12	58	M	75	56	Fair	Duodenal ulcer	20 yr.	Normal	Spinal	38	200	3.54	Good	B
13	67	F	90	80	Poor	Cholecystitis	7 yr.	Normal	Spinal	44	200	4.20	Death in operating room	B
14	53	M	72	58	Fair	Gastric carcinoma	4 mo.	Normal	Spinal	32	200	4.25	Good	B
15	27	F	81	79	Good	Cholecystitis	3 mo.	Normal	Spinal	58	200	5.79	Good	B
16	65	F	67	67	Good	Cholecystitis	12 mo.	Normal	Spinal	35	200	6.70	Nausea and vomiting	B
17	54	F	72	72	Good	Cholecystitis	4 yr.	Normal	Spinal	35	200	7.56	Nausea and vomiting	B

	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
	39	35	35	55	51	59	36	65	77	69	69	63	51	69	28	58
	F	F	M	M	F	M	M	F	M	M	F	F	F	F	F	F
	12	70	96	72	56	73	75	81	55	78	72	50	16	66	45	76
	45	70	60	41	56	60	60	72	13	60	56	50	34	62	45	78
	Good	Good	Poor	Poor	Good	Poor	Poor	Poor	Poor	Poor	Fair	Poor	Poor	Poor	Good	Good
	Cholecystitis	Cholecystitis	Gastric carcinoma	Gastric carcinoma	Cholecystitis	Obstructive jaundice	Obstructive jaundice	Obstructive jaundice	Gastric carcinoma	Gastric carcinoma	Cholecystitis	Cholecystitis	Duodenal ulcer	Carcinoma of gall bladder	Cholecystitis	Hypertension
	3 yr.	13 yr.	7 mo.	7 yr.	3 yr.	10 wk.	5 mo.	5 mo.	2 yr.	9 mo.	4 yr.	45 days	3 mo.	8 mo.	12 mo.	9 yr.
	Normal	Normal	Normal	Normal	Normal	Advanced damage	Advanced damage	Advanced damage	Advanced damage	Moderate damage	Slight cirrhosis	Slight cirrhosis	Normal	Moderate damage	Normal	Normal
	N <sub>2</sub> O and ether	N <sub>2</sub> O and ether	N <sub>2</sub> O and ether	N <sub>2</sub> O and ether	N <sub>2</sub> O and ether	Spinal	Spinal	N <sub>2</sub> O and ether	Spinal	Spinal	Cyclopropane	Local	N <sub>2</sub> O and ether	Cyclopropane and N <sub>2</sub> O	Cyclopropane	Spinal
	31	90	70	30	90	25	42	105	25	14	45	30	18	86	38	235
	200	200	200	200	200	200	200	200	200	0	200	200	0	200	0	0
	3.91	4.17	4.82	4.98	5.75	2.70	2.74	2.91	3.14	1.22	4.14	4.40	4.45	4.48	4.65	5.56
	Good	Fair	Good	Fair	Good	Good	Death 14 days post-operatively	Fair	Poor	Good	Good	Fair	Good	Death 8 days post-operatively; hepato-renal syndrome	Good	Good
	C	C	C	C	C	D	D	D	D	E	E	E	E	E	E	E

received approximately the same preoperative medication, and the biopsies were taken at approximately the same time of day.

*Percentage of Glycogen in Cases With Normal Livers.*—Group A in Fig. 1 shows the distribution of values in percentage of liver glycogen for 10 patients whose general condition with one exception was fair or good. These patients all were operated upon under spinal anesthesia, their livers were normal to both gross and microscopic examination, and none of these patients received supplementary glucose feedings. The average percentage for this good group undergoing a major operative procedure was 3.15; the range from 1.1 to 6.31 per cent.

Group B, in contrast to Group A, had conditions of general health, diagnosis, liver histology, and anesthesia similar to Group A, but in addition received supplementary feedings of glucose which were given in divided doses of 50 Gm. of glucose in 30 c.c. of lemon juice, two doses in the evening and two doses in the morning before operation. The average percentage of their liver glycogen was 5.03; the values ranged from 3.19 to 7.56. The lowest value for Group B was slightly higher than the average for the patients in Group A, who did not receive the supplementary glucose feedings. On the basis of average percentage alone, Group B showed a 60 per cent increase over Group A.

Group C consists of 5 patients who were operated upon under nitrous oxide and ether anesthesia, and whose livers were found to be normal. All of these patients received supplementary glucose feedings and their average hepatic glycogen content was 4.72 per cent, which is slightly lower than the average for similar patients operated upon under spinal anesthesia.

*Percentage of Glycogen in Cases With Liver Damage.*—The ability of a damaged liver to store glycogen is shown by Group D in Fig. 1 in which are placed 4 patients with advanced hepatic pathology. The operations were performed either under spinal or nitrous oxide and ether anesthesia. All 4 cases received 200 Gm. of glucose in the twelve hours immediately preceding the operation. Here the average percentage of hepatic glycogen for the 4 cases was 2.87, which is only about one-half the average value obtained in cases that had normal livers. This demonstrates the apparent inability of damaged livers to synthesize and store glycogen in as large amounts as the normal liver. We feel that the levels of glycogen found in these patients with damaged livers probably represent nearly maximum values, since all 4 patients were hospitalized at least five days prior to their operation and received a high carbohydrate, low fat diet during that time and in addition were given supplementary glucose feedings up to within three hours before their operation, thus tending to avoid the drop in hepatic glycogen due to fasting which is most marked in high carbohydrate fed animals.

*Changes in Liver Glycogen During Operations Under Spinal Anesthesia.*—Table II shows the variations during operation of the glycogen content of the human liver. As can be seen, with the exception of



TABLE II  
CHANGES IN LIVER GLYCOGEN DURING OPERATIONS UNDER SPINAL ANESTHESIA (17 C.C. 1:1,500 NUPECAINE)

PATIENT NO.	PERCENTAGE GLYCOGEN		DIFFERENCE BETWEEN GLYCOGENS	TIME BETWEEN BIOPSIES (MIN.)	SUPPLEMENTARY GLUCOSE FEEDING IN 12 HRS. PRE-OPERATIVELY (GMC.)	DIAGNOSIS	ESTIMATE OF GENERAL HEALTH	LIVER HISTOLOGY	POSTOPERATIVE COURSE
	FIRST BIOPSY	SECOND BIOPSY							
2	1.99	1.00	-.39	68	0	Duodenal ulcer	Fair	Normal	Fair
3	2.32	0.96	-1.36	70	0	Duodenal obstruction	Poor	Normal	Death 4 days post-operatively
4	2.48	3.10	.62	56	0	Cholecystitis	Good	Normal	Good
5	3.12	3.00	-.12	142	0	Gastric carcinoma	Fair	Normal	Good
8	3.68	3.79	.11	27	0	Cholecystitis	Good	Normal	Good
10	6.31	5.61	-.67	33	0	Cholecystitis	Good	Normal	Good
13	4.20	4.79	.59	34	200	Cholecystitis	Poor	Normal	Death in operating room
27	1.22	1.85	.63	11	0	Gastric carcinoma	Poor	Moderate damage	Good

received approximately the same preoperative medication, and the biopsies were taken at approximately the same time of day.

*Percentage of Glycogen in Cases With Normal Livers.*—Group A in Fig. 1 shows the distribution of values in percentage of liver glycogen for 10 patients whose general condition with one exception was fair or good. These patients all were operated upon under spinal anesthesia, their livers were normal to both gross and microscopic examination, and none of these patients received supplementary glucose feedings. The average percentage for this good group undergoing a major operative procedure was 3.15; the range from 1.1 to 6.31 per cent.

Group B, in contrast to Group A, had conditions of general health, diagnosis, liver histology, and anesthesia similar to Group A, but in addition received supplementary feedings of glucose which were given in divided doses of 50 Gm. of glucose in 30 c.c. of lemon juice, two doses in the evening and two doses in the morning before operation. The average percentage of their liver glycogen was 5.03; the values ranged from 3.19 to 7.56. The lowest value for Group B was slightly higher than the average for the patients in Group A, who did not receive the supplementary glucose feedings. On the basis of average percentage alone, Group B showed a 60 per cent increase over Group A.

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*Percentage of Glycogen in Cases With Liver Damage.*—The ability of a damaged liver to store glycogen is shown by Group D in Fig. 1 in which are placed 4 patients with advanced hepatic pathology. The operations were performed either under spinal or nitrous oxide and ether anesthesia. All 4 cases received 200 Gm. of glucose in the twelve hours immediately preceding the operation. Here the average percentage of hepatic glycogen for the 4 cases was 2.87, which is only about one-half the average value obtained in cases that had normal livers. This demonstrates the apparent inability of damaged livers to synthesize and store glycogen in as large amounts as the normal liver. We feel that the levels of glycogen found in these patients with damaged livers probably represent nearly maximum values, since all 4 patients were hospitalized at least five days prior to their operation and received a high carbohydrate, low fat diet during that time and in addition were given supplementary glucose feedings up to within three hours before their operation, thus tending to avoid the drop in hepatic glycogen due to fasting which is most marked in high carbohydrate fed animals.

*Changes in Liver Glycogen During Operations Under Spinal Anesthesia.*—Table II shows the variations during operation of the glycogen content of the human liver. As can be seen, with the exception of

factor against liver damage is not definitely known although a specific action of methionine has been suggested.<sup>55</sup> Mirski and his associates<sup>55</sup> believe that it is due to intensified glycconeogenesis. Goldschmidt and his co-workers<sup>53</sup> explain the protective action of a high protein diet as 'primarily the result of protein available to the liver as a result of the high protein intake.' They do not believe that the hepatic glycogen is a factor in preventing liver injury due to chloroform. A high protein diet may be contraindicated in cases which have definite hepatic pathology, since Bollman and Mann<sup>52</sup> have shown that the survival time and general well-being of a dog with obstructive jaundice are increased when fed a high carbohydrate diet, and diminished when fed a high protein diet. Moise and Smith<sup>48</sup> demonstrated that the most active regeneration of liver tissue occurred when the subject was fed a well-balanced stock diet. Stone<sup>42</sup> confirmed this but also found that a high carbohydrate diet was almost as effective, while a high protein diet showed considerably less regeneration of the liver.

Whether or not the protection of the liver from damage due to specific hepatic toxins and its subsequent regeneration is a matter of protein or carbohydrate feeding, and there is evidence of value for both, the practical point is the relative ease with which the carbohydrate intake can be markedly increased just prior to operation. In our patients, supplementary glucose feedings in the twelve hours before the operation raised the glycogen content of the normal livers. In the damaged livers the hepatic glycogen value averaged 2.87 per cent compared to 3.15 per cent for normal livers not receiving supplementary glucose feedings. We feel that 2.87 per cent is a fair value considering the severe degree of liver damage present in our cases. This study helps to confirm the opinion which has long been expressed by many surgeons on the supportive value of a well-chosen preoperative diet in decreasing the stress of long, severe operations and of sustaining the bad risk patient.<sup>56, 57</sup>

#### SUMMARY

Biopsies were taken from the liver of 33 patients during their operations and the percentages of glycogen in the liver were determined. The average hepatic glycogen found was 3.96 per cent and the values ranged from 1.1 to 7.56 per cent. Observations were made according to the following groups:

*Group A.*—The average value of hepatic glycogen in patients with normal livers operated upon under spinal anesthesia was 3.15 per cent. The lowest value was 1.1 and the highest was 6.31 per cent.

*Group B.*—When supplementary glucose feedings were given to patients with normal livers in the twelve hours preceding an operation carried on under spinal anesthesia, the average hepatic glycogen rose to 5.03 per cent and the values ranged from 3.19 to 7.56 per cent. Sup-

Case 3, no significant change in the hepatic glycogen occurred during operation, even after the longest time interval of 142 minutes between the biopsies had elapsed. All patients were given the same preoperative medication, morphine sulfate  $\frac{1}{4}$  gr. and scopolamine  $\frac{1}{200}$  gr. The patient who did show a significant drop, Case 3, did not do well at any time after the operation, which was followed by shock. Her course was gradually downhill and respiration ceased on the fourth postoperative day, the final cause of death being massive left pulmonary atelectasis. One of the patients, Case 13, died of a pulmonary embolism while on the operating table. The other patients did well following their operation.

*Relation of Liver Glycogen to Postoperative Course.*—We cannot state whether or not those cases with high liver glycogen had the best postoperative courses. Nineteen had an uneventful postoperative convalescence without fever, nausea, vomiting, or other complications. The average amount of glycogen for this group was 4.04 per cent. Nine patients had fair postoperative courses; that is, they either had temperatures elevated above  $100^{\circ}$  F., or had nausea, vomiting, or other mild complications. The average percentage of glycogen for this group was 4.11 per cent. Four patients had very poor, stormy, postoperative courses, and their hepatic glycogen averaged 3.17 per cent. The lower percentage of glycogen found in these 4 patients may be significant, but no definite conclusions can be drawn because of the small number of cases studied and the many variable factors involved. The postoperative course of any patient may be upset by numerous factors unrelated to liver glycogen. But in the care of the seriously ill patient food elements cannot be neglected and the value of a high carbohydrate diet in preventing liver damage from specific hepatic toxins and its efficacy in the treatment of hepatic disease has been well shown in animal experiments. Roger,<sup>39</sup> in 1887, first demonstrated the value of glucose in the detoxification of phosphorus by the livers of animals. Beddard,<sup>40</sup> in 1908, first suggested its use in chloroform poisoning. Opie and Alford,<sup>41</sup> in 1915, were the first to show experimentally that a diet high in carbohydrate gives protection against liver damage due to chloroform and phosphorus. Since then their work has been confirmed in the laboratory.<sup>42-53</sup>

That a high carbohydrate diet with a resulting high hepatic glycogen is not the only factor involved in the prevention of liver damage is well known, and that protein is just as important, if not more so, has also been experimentally established. Goldschmidt, Vars, and Ravdin<sup>54</sup> have shown that the severity of liver damage due to chloroform poisoning is primarily dependent on the concentration of lipids in the liver. They believe that the value of a high carbohydrate diet is due to its action in decreasing the amount of lipids in the liver and also due to its protein sparing action. The manner in which a high protein diet acts as a pro-

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plementary glucose feedings thus increased the average liver glycogen of Group B 60 per cent over that of the control Group A. This should be of definite value in lessening the stress of long, severe operations and in sustaining the bad-risk patient.

*Group C.*—When supplementary feedings were given to patients with normal livers in the twelve hours preceding an operation carried on under nitrous oxide and ether anesthesia, the average hepatic glycogen value was 4.72 per cent, and the range 3.91 to 5.75 per cent. This average was slightly lower than a similar group (Group B) operated upon under spinal anesthesia.

*Group D.*—With supplementary glucose feedings 4 patients with advanced liver damage showed an average hepatic glycogen of 2.87 per cent and a range of 2.7 to 3.14 per cent.

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reported the bacteria found in the gall bladder wall and its contents in 92 cases; the wall was sterile in 57 per cent and the contents were sterile in 67 per cent. *Bacillus coli* was present in the wall in 11 per cent and in the contents in 16 per cent. In 4 cases with obstruction of the common duct, *B. coli* was isolated in 1 case, and *B. coli* and *B. welchii* together in the other 3. If the cystic duct was closed, the acute cases gave positive cultures in 8 of 11 cases, but in the chronic group, the cultures were sterile in 9 out of 10 cases.<sup>5</sup> Andrews' bacteriologic findings indict the *B. coli* as the organism associated with most of his postoperative disasters. It was found in 9 cases; in 3 instances the patients died; a fourth patient developed a large postoperative abscess in the gall bladder bed; in the fifth patient profuse wound suppuration occurred resulting in hernia; the sixth patient had a fever of 105° F. following cholecystectomy; the seventh patient nearly died of paralytic ileus and enormous distention.<sup>3</sup>

Hanssen and Yurevich<sup>6</sup> in 1935 reported the organisms cultured from the biliary tract in 104 cases at operation; 67 per cent were sterile and 33 per cent were infected. The location of the organisms in the infected cases was gall bladder wall, 85.2 per cent; gall bladder bile, 59 per cent; cystic duct node, 38 per cent; gallstones, 24 per cent. In 10 of the 34 infected cases the organism present was the *B. coli*. Haussen and Yurevich collected the results of cultures of the biliary tract reported by others; *B. coli* was present in from 5 to 54 per cent of the infected biliary tracts. Mailer<sup>7</sup> in the examination of fifty surgically removed stone-bearing gall bladders found *B. coli* in 5 cases.

Aronsohn's experiments<sup>8</sup> in animals indicate that an increase in the number of bacteria in bile seldom produced a reaction in the gall bladder wall when the technique was nontraumatizing. However, in many cases the same organisms injected through the gall bladder wall directly or with accompanying ligation of the common or cystic duct produced severe or even fatal cholecystitis. The latter findings and the bacteriologic findings of Andrews appear to indicate that infection does not become a significant factor in many instances of biliary tract disease unless there is an accompanying erosion of the gall bladder wall by stones or obstruction to the outflow of bile.

Considerable evidence has been brought forth that cholecystitis is not by any means always an infectious process.<sup>9</sup> The stressing of chemical, mechanical, vascular, toxic, and anatomic factors in the initiation of many of the acute gall bladders should not permit one to lose sight of the fact that infection may be superadded and that there is a fair number of acute gall bladders which are of the purely infected type from beginning to end.

How does the infection in the biliary tract cause the septicemia? Is the biliary tract infection a localization of a sepsis originating from some other focus? In experimental septicemia Chabrol and his asso-

# COLON BACILLUS SEPTICEMIA ASSOCIATED WITH ACUTE CHOLECYSTITIS

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COLON bacillus septicemia itself is not common, and its association with acute biliary tract disease has been described very infrequently in recent medical literature. The present study is based upon three cases of colon bacillus septicemia associated with acute cholecystitis encountered within a period of fourteen months. Individually these cases presented clinical pictures which made the diagnosis difficult. On reviewing the group certain clinical aspects appeared, which deserve emphasis because of their diagnostic value.

Colon bacillemia may occur in three forms: (1) as an acute and persistent septicemia from the outset; (2) as a temporary bacillemia immediately after trauma, surgical or otherwise, to an area infected with colon bacilli; and (3) as a terminal bacillemia.

The cases to be described are of the first type, an acute colon bacillus septicemia with signs pointing to the gall bladder as the portal of entry. A positive blood culture was obtained in each case prior to operation; hence this was not the fleeting bacillemia which may occur after traumatizing an infected focus, as might be the case if the cultures were taken immediately after operation. Nor was the bacillemia a terminal phenomenon, since two patients are living and well, and the third lived for thirty-five days after the first positive culture.

The infrequency of colon bacillus sepsis may be inferred from the meager literature on the subject. In 1909 Jacob<sup>1</sup> was able to collect but 36 cases from the literature. To these he added 13 of his own. In 3 of his 13 cases and in 15 of the 36 collected cases the biliary tract was indicted as the primary focus. In 1924 Felty and Keefer<sup>2</sup> reported 28 cases of colon bacillus septicemia and reviewed the literature to that date. They were able to identify the portal of entry as urinary, genital, intestinal, or a wound. In none of their cases was the origin from the biliary tract. Since 1924 we have found 39 cases of colon bacillus sepsis reported in the literature.<sup>3</sup> Nine of these cases were apparently associated with acute lesions in the biliary tract such as acute cholecystitis, common duct obstruction, or cholangitis.

## RELATIONSHIP OF COLON BACILLUS TO BILIARY TRACT DISEASE

The role of bacteria in the biliary tract may vary from that of innocuous residency to virulent invasion. Andrews and Henry<sup>4</sup> in 1935

Summaries of case reports of colon bacillus septicemia associated with acute lesions in the biliary tract in the available literature from 1924 to 1939:

Simon<sup>3a</sup> reported 2 cases of colon bacillus septicemia. The first patient was a female, 63 years of age, who became ill with nausea and vomiting, and then developed jaundice accompanied by chills and fever. She was admitted to the hospital three weeks after the onset. Physical examination at that time showed some enlargement of the liver, red nodules on the legs, and evidence of a peripheral neuritis. The blood culture showed colon bacilli. The leucocyte count ranged from 4,000 to 13,600. There was no elevation of the blood bilirubin. She became progressively worse and was operated upon. A mild pericholecystitis without stones was found, and cholecystectomy was performed. Her fever subsided two days after the operation and she recovered.

The second patient was a female, 50 years of age, who had suffered from cholecystitis for several years. For fourteen days before admission she had severe pain in the right upper abdomen, jaundice, dark urine, light stools, chills and fever. After eight days the right arm suddenly became paralyzed. The pain became milder and the patient became stuporous. On admission the patient was comatose and jaundiced. The abdomen was not tender, the liver was palpable in the midline. The urine showed albumin and casts and was positive for urobilinogen. Blood: RBC, 2,700,000, Hgb, 48 per cent; WBC, 13,200, 16 per cent young forms. Three days later the leucocyte count was 9,000, 54 per cent young forms. Van den Bergh test: direct positive reaction. The fever varied from 36.9 to 39.7° C. The patient died four days after admission. Post-mortem examination disclosed dense adhesions between the stomach and gall bladder with a gastrobiliary fistula. A suppurative cholangitis was present, the pus containing *B. coli* in pure culture. There were multiple brain abscesses, the pus containing *Staphylococcus aureus* and *B. coli*, the latter predominating.

Simon and Criz<sup>1b</sup> reported colon bacillus sepsis in a male 20 years of age. The onset was sudden and accompanied by vomiting, epigastric pain, and headache. He gave a history of two previous similar attacks. On admission the temperature was 38° C. The abdomen was slightly tender and rigid in the right upper quadrant. The leucocyte count varied from 15,000 to 21,600. The patient became progressively worse and died shortly after admission. The blood culture made eight hours ante mortem showed *B. coli*. The clinical diagnosis was cholecystitis, cholelithiasis, and acute hepatitis. At post-mortem the original focus of infection was found to be in the biliary tract.

Hofel<sup>1</sup> reported colon bacillus septicemia in a male 51 years of age. The onset occurred three or four days before admission. There was malaise, pain in the liver area, and a fever up to 39° C. On the day before admission the patient became stuporous and jaundiced. On physical examination the jaundice and stupor were seen and there were

ciates<sup>10</sup> have shown that organisms injected intravenously are excreted by the liver and the kidney in the first six to eight hours.

When there is biliary obstruction, the liver defense against sepsis diminishes, and organisms which would ordinarily have been eliminated rapidly might stay longer in the circulation. One would also expect an accumulation of organisms behind an obstruction in the common duct, and Andrews' findings<sup>2</sup> bear this out.

Lengupta's experiments<sup>11</sup> with intravenously injected colon bacilli possibly elucidate the pathology of the enormous thickening of the gall bladder wall seen in many acute cases but do not indicate an explanation for the sepsis. Intravenous injection of *B. coli* in a normal animal leads to an accumulation of bacteria in the liver and capillary thrombi. In the sensitized, vaccinated, or reinjected animal there is rapid lysis of the injected organisms without definite cellular reaction; the Kupfer star cells do not react. Repeated hematogenous infection of the liver and biliary tract leads to chronic irritation of the gall bladder and biliary tract in which there is infiltration with large lymphocytes and thickening of the walls.

The venous drainage from the gall bladder is into the portal system. When the gall bladder is a focus of infection with *B. coli*, huge numbers of bacteria are probably being poured into the liver directly rather than into the general circulation, as would be the case with a focus in the urinary tract or genital tract. Thus the liver defense may be overwhelmed. This may be the explanation for the extremely toxic condition of these patients.

Patey and Whitby<sup>12</sup> injected bacteria into the portal vein and found the organisms in the general circulation after a few minutes. This would suggest that the liver is only part of the defense against the organisms which enter the portal circulation from the intestine, and that a septic focus draining into the portal system as does the gall bladder may cause a septicemia almost as readily as a septic focus elsewhere; but in most cases the organisms and their toxins are filtered out in the liver and may never reach the general circulation in sufficient numbers for them to be found in blood culture as would be the case if the septic focus were elsewhere.

Colon bacillus infection of the duodenum may have some relationship to biliary tract infection. Grunke<sup>13</sup> was able to recover *B. coli* from the duodenum in 48 per cent of 121 patients presenting symptoms of biliary tract involvement. Colon bacillus infection of the duodenum is most common beyond the age of 40 years; only 11 of 130 cases occurred under the age of 40 years. Similarly the majority of the patients with colon bacillus septicemia associated with cholecystitis are more than 40 years of age. Thus there is a striking parallelism in the age groups of colon bacillus septicemia, associated with cholecystitis, and colon bacillus infection of the duodenum, both are most frequent beyond the age of 40 years.

*Past Medical History.*—Diabetes mellitus for three years, an attack of biliary colic six months before, dyspnea on exertion for some time, and recurrent backache for the past six months.

*Physical examination* showed a well-nourished male, drowsy, cyanotic, and dyspneic. Rectal temperature, 104.4° F.; pulse rate, 136; respirations, 42; blood pressure, 114/84. The nasopharynx showed evidence of an acute ethmoiditis. Chest: Fine crepitant rales were found at the bases of both lungs with diminution of resonance. Abdomen: Moved with respiration, reflexes present, no palpable masses, no definite tenderness, no rigidity of the muscles except for an increase in resistance to pressure in the right upper quadrant, and marked diffuse distention. Urine: Acid, specific gravity, 1.011; trace of albumin; sugar, 1.1 per cent, acetone, plus 2; W.B.C. 2 to 3; occasional fine and coarsely granular casts; occasional hyaline casts. Blood: Hb., 100 per cent; R.B.C., 5,260,000; W.B.C., 33,800 with 92 P.M.N. (44 nonsegmented, 48 segmented); blood sugar, 300; urea nitrogen, 19.6; CO<sub>2</sub> combining power, 54 volumes per cent.

Tentative diagnosis on admission: lobar pneumonia, diabetes mellitus, myocardial impairment, chronic biliary tract disease. The abdominal signs appeared to be accounted for by the pulmonary pathology.

Chest x-ray on the day of admission showed no evidence of pulmonary consolidation or pleural effusion, and the diaphragms were normal. A blood culture made on the same day showed a growth of *B. coli*. An electrocardiogram indicated severe myocardial disease.

The patient was treated by administration of glucose and saline solution parenterally, insulin, oxygen, and other supportive medication. Small amounts of carbohydrates were given orally. From April 5 to April 9, 1937, his condition improved. The temperature, pulse, and respiratory rate fell to 100.6° F. rectally, 90, and 26, respectively, and the abdominal distention subsided. Another blood culture showed *B. coli*.

On April 10 he again became drowsy and restless and the temperature rose. On April 11 he became more toxic and irrational and the temperature rose to 104.6° rectal. Abdominal examination disclosed only some resistance in the right upper quadrant. There was no evidence of a lesion acute enough to account for the septicemia, although a biliary lesion was considered. A transfusion was given. Chest x-ray showed no changes except for a few small, poorly defined areas suggesting early bronchopneumonia. On April 12 his condition became even worse and he appeared to be in extremis. Abdominal examination now disclosed a mass in the region of the gall bladder. A scout x-ray film of the abdomen showed only gaseous distention of the stomach. A cystoscopy done to exclude a lesion of the right kidney was negative. After another transfusion the patient was subjected to an exploratory operation under local anesthesia. An acute gangrenous cholecystitis was found. The gall bladder had perforated, and abscesses had formed contiguous to it in the liver. The gall bladder was removed, clamps being left on the cystic duct, artery, and some smaller vessels because the tissues were too necrotic to hold ligatures. The wound was packed.

The patient was practically moribund. He improved slightly after a transfusion in the evening, and after another transfusion on the following day he was definitely on the mend.

Culture of the cystoscopic urine showed *B. coli* and culture of the bile obtained at operation showed *B. coli* and *B. welchii*.

Attempts to prepare a bacteriophage for the colon bacillus failed. Blood cultures made on April 14 and on April 19 showed no growth. Treatment was continued by parenteral fluids; insulin, etc., and carbohydrates by mouth were started late on April 13. By April 15 he was definitely out of danger, and the clamps in the wound were removed. There was no hemorrhage, but there was marked drainage of purulent material which decreased daily. Another transfusion was given

convulsions. Aside from slight enlargement of the liver there were no palpable lesions of the biliary tract. The leucocyte count was 16,200 and the blood culture was positive for colon bacillus. The patient died one day after admission and at the post-mortem examination an acute cholangitis was found.

May and Boulin<sup>31</sup> reported a case of colon bacillus septicemia in a patient with severe jaundice simulating acute infectious jaundice (spirochetosis icterohaemorrhagica). The etiology was not determined.

Melnotte, Pierre, and Farjot<sup>32</sup> reported a case of colon bacillus septicemia accompanied by jaundice and intermittent fever.

Lenierre, Angier, and Mahoudeau-Campoyer<sup>33</sup> reported colon bacillus septicemia in a male 74 years of age. The patient became ill six days before admission, complained of severe pain in the right upper quadrant of the abdomen and of chills. The examination on admission showed jaundice and a mass in the right upper quadrant. Temperature was 38.5° C. Urobilinuria was present and a blood culture made two days after admission showed the colon bacillus. Three days after admission the patient improved and the temperature became normal. No operation was performed.

Garcia<sup>34</sup> reported colon bacillus septicemia in a female 38 years of age. The onset was abrupt and accompanied by chills and fever (101 to 103° F.). Physical examination showed tenderness and a mass in the right upper quadrant of the abdomen. Leucocyte count was 8,000 to 9,000. The patient was treated by biliary drainage by mouth and recovered without complications.

Davis and Turner<sup>35</sup> reported a colon bacillus septicemia in a female 35 years of age. About two years prior to admission she had been subjected to operation for stones in the gall bladder and common bile duct. The gall bladder had been removed and the common duct had been cleared of all stones and drained by a rubber tube. Recovery was uneventful. One day before admission the patient was seized with violent upper abdominal pain, vomiting, and fever (103.2° F.). After admission she developed slight jaundice and violent chills, and repeated blood cultures showed colon bacilli. Colon bacilli in pure culture were repeatedly found in the urine. Injections of colon bacillus vaccine were given. X-ray of the abdomen disclosed many small calculi in the common bile duct. The patient refused operation after the symptoms subsided and was discharged twenty-three days after admission.

#### CASE REPORTS

CASE 1.—Dr. W. W., aged 46 years, a physician, was admitted on April 5, 1937, complaining of malaise, fever, and abdominal pain. He gave the following history: He had been in good health until April 2, 1937, when he began to have pain in the right upper quadrant of the abdomen, suggestive of biliary colic, and accompanied by an elevation of temperature to 102° F. The pain disappeared in about twenty-four hours, but the fever persisted. He became toxic and drowsy and was taken to the hospital.

CASE 3.—Mrs. J. R., aged 65 years, was admitted to the hospital on June 5, 1938, complaining of fever and pain in the back. She gave the following history: She had been well until one week before admission, when she began to have chills, fever, and sweats, said by her physician to resemble those of malaria. These recurred daily. On the day before admission she began to have pain in her back, which persisted. There had been no respiratory, gastrointestinal, or urinary symptoms.

Physical examination showed an elderly white female, dyspneic, and exhibiting marked cyanosis. Temperature, 102.4°; pulse rate, 140; respirations, 30, blood pressure, 170/74. Head, negative, except for slight fetor oris. Chest: a few rales in the left lung base, auricular fibrillation with pulse deficit. Abdomen: marked distention, palpation very difficult. Liver palpable, slightly below the costal margin. An umbilical hernia of moderate size, reducible, was present. Tentative diagnosis on admission: Septicemia of unknown origin, possible pyelitis, hypertensive cardiovascular disease, umbilical hernia. Urine: acid, specific gravity, 1.010; trace of protein; 8 to 10 W.B.C.; occasional R.B.C.; very occasional hyaline and fine granular casts. Blood: Hb., 90 per cent; R.B.C., 4,660,000; W.B.C., 23,700; polymorphonuclears, 89 per cent; blood sugar, 100; blood urea nitrogen, 31; icterus index, 18; van den Bergh test, very faint biphasic reaction. A blood culture made on June 6 showed *B. coli*.

The patient had chills and fever for the next few days. The abdominal findings were practically nil until June 9, when marked tenderness and rigidity were noted in the right upper quadrant. Jaundice became visible. Sulfanilamide gr. xx four times daily had been started on June 5. It was discontinued on June 9.

The patient was given glucose parenterally and was then operated upon without further delay (June 9). Under local anesthesia, supplemented by small amounts of nitrous oxide and oxygen, a right subcostal incision was made. The gall bladder was gangrenous and had perforated. The necrotic gall bladder was removed down to the ampulla, into which was fixed a rubber tube. A gauze drain was placed in the hepatic gall bladder bed.

*B. coli* was isolated from the bile removed at operation. Anaerobic cultures showed no anaerobes. Immediately following operation the patient received a transfusion and glucose and saline solution parenterally. In the next few days her temperature remained high (103 to 104°). She then improved and a transfusion was given on June 11. On June 12 her jaundice was much less, her heart was not fibrillating, and she was taking liquids well. The wound was draining profusely. Abdominal x ray (scout film) on June 4 showed considerable gaseous distention of the stomach with slight gaseous distention of the transverse colon. The diaphragms appeared normal.

On June 16 she became worse. A blood culture showed no growth. For the next few days she again had chills. Her condition continued septic and downhill. On June 20 another blood culture showed no growth. On June 23 chest x ray showed no abnormalities of the lungs or diaphragm. Blood culture on June 25 showed no growth. On June 25 the draining sinus was injected with sodium iodide. X ray showed a tract 12 cm in length and 1 cm wide and gave no other information. Another transfusion was given on June 30. Her condition continued unchanged except for a moderate fall in the level of fever. On July 5 a transfusion was given. On July 6 the fever increased and by July 10 the level was 103 to 104°. No definite focus of suppuration could be identified. A subhepatic suppuration was suspected, and since the patient was still losing ground, the wound was opened under nitrous oxide anesthesia on July 12. No definite lesion was found. Early on the following morning she had an abrupt rise in temperature (105 rectally) and pulse rate (160). The blood pressure was 85/70. She became irrational and pulseless and died about twenty-four hours after her second operation. Blood culture taken July 10 was negative.

on April 16, and he proceeded to recover without any further complications. On April 27 he was allowed out of bed, the temperature being almost normal, and on May 11 he was discharged in good condition.

Pathologist's report on the gall bladder: "Gangrenous cholecystitis with suppurative pericholecystitis."

CASE 2.—S. M., a white male, 48 years of age, was admitted on May 2, 1937, complaining of fullness and discomfort in the upper abdomen for three days and an acute attack of epigastric pain, nausea, and vomiting for two and one-half hours.

*History.*—He had been in his usual health until three days previously, when he awoke feeling "out of sorts." Following breakfast he developed a marked sense of fullness and distress in the upper abdomen with some reference to the right shoulder. Later in the day he was given an enema and a saline purge. He felt somewhat improved until 7:00 p.m. on the night of admission when he again began to have epigastric discomfort and pain which became progressively more severe. Nausea and vomiting followed. His physician had him taken to the hospital immediately.

*Physical examination* showed a well-developed, dark-complexioned middle-aged male, drowsy, and apparently acutely ill. Temperature, 101° F.; pulse, 120; respirations, 20; blood pressure, 120/80; head, neck, and chest were negative. The significant findings were abdominal; a marked distention with a tense abdominal wall. Determination of tenderness was unsatisfactory because of prior administration of morphine. A marked increase in muscle tonus was present in both upper quadrants. Peristalsis was heard throughout. The abdominal reflexes were absent. Urine: acid, specific gravity, 1.021; very faint trace of albumin; 2 to 4 W.B.C. Blood: W.B.C., 16,400; polymorphonuclears, 87 per cent.

Tentative diagnosis: cystic duct obstruction with acute suppurative cholecystitis.

Symptomatic treatment was given. On the following day (May 3) the temperature remained about 102° F. He felt slightly improved. An electrocardiogram indicated myocardial damage but no infarction. Blood count: Hb., 90 per cent; R.B.C., 4,540,000; W.B.C., 10,250; polymorphonuclears: 91 per cent.

On May 4 abdominal x-ray showed a distention distal to the hepatic flexure, indicating a colon lesion at that point or a lesion in the right upper quadrant. A blood culture was reported positive for *B. coli*. The abdominal pain became much more severe. Physical examination of the abdomen at this time disclosed a very tender tense mass in the right upper abdomen. At noon there was a severe chill with a rise in temperature to 105° F. A diagnosis of gangrenous cholecystitis was made and an emergency operation was performed about 5:00 p.m. after the administration of glucose and saline solution.

Under spinal and nitrous oxide anesthesia a right subcostal incision was made and a large distended gall bladder was exposed. The liver was dark and large. The gall bladder was aspirated and then removed after ligation and division of the cystic duct and artery. A gauze drain was put down to the gall bladder fossa of the liver and the abdomen was closed. Subsequently culture of the gall bladder bile showed *B. coli*. Anaerobic culture showed no anaerobes.

The patient received a transfusion of 300 c.c. of whole blood immediately after operation. Sufficient glucose and salt solution was given in the following thirty-six hours. On May 5 (the day after operation), catheterization was necessary. On May 6 the temperature dropped to 100° and a slight jaundice developed. Blood: Hb., 100 per cent; W.B.C., 17,900; polymorphonuclears, 84 per cent; sugar, 198; urea, N. 24.2; chlorides, 524; icterus index, 12.8. The symptoms cleared up promptly and the temperature was normal on May 9. He was discharged on May 17 in good condition. Pathologist's report on gall bladder: Wall average in thickness, mucosa appeared normal. Microscopic examination: "Chronic cholecystitis."



convulsions. Ordinarily the colon bacillus is not of great virulence, so that the toxemia seems disproportionate. It may perhaps be due to toxic hepatitis with impairment of the detoxifying function of the liver and in part to dehydration.

It might be expected that such a violent infection within the abdomen would be clearly manifested by abdominal symptoms and signs. This is not the case. The abdominal symptoms may be masked by toxemia and drowsiness or coma, and the signs may be masked by distention of the colon and slight reflex rigidity. Case 1 on admission showed a diffuse abdominal distention and a very slight increase in resistance to pressure in the right upper quadrant. Definite signs pointing to the gall bladder, a tender mass in the right upper quadrant, did not appear until seven days after admission. Case 2 on admission exhibited marked abdominal distention and an increase in tension of the abdominal muscles, mainly in the upper quadrants. Two days later a tender mass was found in the right upper quadrant. Case 3 on admission also showed striking abdominal distention. There were no other signs except for a palpable liver. Not until four days later did tenderness and rigidity appear in the right upper quadrant. In retrospect, the significant finding was the distention.

The laboratory findings include not only blood cultures positive for *B. coli* in the three cases, but also cultures of *B. coli* from the gall bladder bile. In Case 1 *B. welchii* was also found in the gall bladder bile. In this case the urine obtained during cystoscopy also showed colon bacilli. The leucocyte counts on admission varied over a wide range: Case 1: 33,800 polymorphonuclears, 92 per cent, 44 nonsegmented, 48 segmented; Case 2: 16,400 polymorphonuclears, 87 per cent; Case 3: 23,700 polymorphonuclears, 89 per cent. Elevation of the icterus index was recorded in 2 cases, and it was probably toxic in origin.

#### DIFFERENTIAL DIAGNOSIS

The relative insignificance of signs pointing to the gall bladder made identification of the true condition very difficult. In Cases 1 and 3 the signs at the lung bases and the abdominal distention suggested early pneumonia, possibly pyelitis, as the cause of the symptoms. The signs at the lung bases were explained later by the biliary lesions. Diaphragmatic irritation or inflammation is common in acute suppurative biliary tract disease, and after perforation of the gall bladder, actual subphrenic suppuration is not rare. The local peritonitis explained the distention.

After the primary focus was removed, the sepsis subsided quite rapidly. In Case 3 the persistent fever was due probably not to sepsis, since repeated blood cultures were negative, but to a purulent collection about the spleen. Metastatic abscesses were identified only in the fatal case, two very small ones in the left renal cortex.

Pathologist's report on gall bladder: "Acute gangrenous perforated cholecystitis; cholelithiasis."

*Autopsy Findings.*—Gastrointestinal tract: stomach, moderately distended; small intestines, moderately distended and covered by a thin layer of exudate; colon, normal; liver and gall bladder, cystic duct dilated; common duct slightly dilated; bile, dark, not purulent; liver, large, no abscesses; microscopic, hemorrhagic hepatitis, widespread, advanced, cloudy swelling, fatty infiltration; spleen, large, soft, pulpy, and dark. A localized collection of pus was present at its root in contact with the pancreas. It was walled off by the splenic surface and the regional fat. Adrenals, medullary degeneration: kidneys, cloudy, swelling in right, left, in addition to cloudy swelling, showed two cortical abscesses 2 mm. and 3 mm. in diameter.

#### COMMENT ON PRESENCE OF *B. WELCHII* IN BILIARY TRACT

The presence of the *B. welchii* in the wall and contents of the biliary tract without the signs and symptoms of gas gangrene has been variously reported. *B. welchii* has been found in normal bile at autopsy. This association was noted by Branch who pointed out that this micro-organism, which is indigenous to areas drained by the portal system, is apparently held in abeyance by healthy living tissues. Andrews regards the *B. welchii* as of no significance, although he notes it may be present in the gangrenous gall bladder. In 210 cases in which gall bladder was removed at operation, Branch found the *B. aerogenes capsulatus* in the wall of the gall bladder in 8 cases; in the bile, in 5 cases; and in the stones, in 7 cases. It was never the predominating organism. The *B. welchii* may, however, in rare instances produce a true gas bacillus infection. Graef and Sturtevant found 9 cases of cholecystitis due to *B. aerogenes capsulatus* reported in the literature and added an additional case with post-mortem findings. Of the 10 patients, 5 recovered and 5 died. (For literature on *B. welchii* and its relation to cholecystitis consult Graef and Sturtevant<sup>14</sup> and Lohr.<sup>15</sup>)

#### COMPOSITE CLINICAL PICTURE

Colon bacillus septicemia associated with acute lesions of the biliary tract starts abruptly in patients who are otherwise in good health. Two of our patients (Cases 2 and 3) were in fairly good health at the time of the onset and had no symptoms referable to the biliary tract. One patient (Case 1) was a well-controlled diabetic who had only a single attack of biliary colic six months before. This was characteristic also of almost all of the cases reviewed in the literature. The first symptom is often pain in the right upper abdomen, which may be very severe, very mild, or rarely so slight as to pass unmentioned, and which may subside rapidly due to gangrene and perforation of the gall bladder (Cases 1 and 3). Chills, high fever, vomiting, and perhaps slight jaundice come on simultaneously or follow in short order. In a few days the patient may become toxic, drowsy, and comatose.

A number of the reviewed cases, as well as our own, exhibited this intense toxemia, accompanied in two or three instances by epileptiform

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## TREATMENT

The most important factor in the treatment of a septicemia is the attack on the primary focus. In these cases identification of the gall bladder as the primary focus was followed by cholecystectomy. An unquestionably moribund patient was thereby saved (Case 1) and prompt subsidence of the infection occurred in Case 2. The fatal termination in Case 3 seems due rather to perforation of the gall bladder and subphrenic abscess than to septicemia. An earlier diagnosis and a prompt operation might have saved this patient.

The value of parenteral administration of fluids to correct dehydration and of transfusion for anemia and its supportive effect must not be underestimated.

## SUMMARY

1. Three cases of colon bacillus septicemia associated with acute cholecystitis have been presented. These cases are characterized by abrupt onset of severe or mild abdominal pain, accompanied by chills, fever, and intense toxemia. After a few days signs pointing to the primary focus in the gall bladder may be so masked as to make diagnosis extremely difficult.

2. The literature on this subject has been briefly reviewed.

3. Prompt cholecystectomy appears to be the treatment of choice.

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the liver. This occurred in the days before a method of coagulating the wound to prevent such a mishap had been devised. The second fatality<sup>6</sup> occurred in a moribund patient whose general condition was too feeble to withstand any further manipulation. In the above collected 2,000 cases there have been 11 instances in which the intestine has been accidentally perforated during the procedure and in no case did any fatality or serious complication develop. Except for a few examples of subcutaneous emphysema no other complications or accidents have been reported.

#### TECHNIQUE

I have been performing peritoneoscopies since early in 1938. The instrument used has been the Ruddock peritoneoscope which has been found satisfactory in every respect but one; namely, it would simplify the taking of biopsies if the biopsy forceps could be fitted with a sliding collar as is the observation telescope. By this means the forceps could be slid back and forth within the metal sheath instead of sliding the sheath through the skin as is now necessary. The examination has always been carried out in a darkened operating room under strict aseptic precautions. The technique has followed that of Ruddock<sup>7</sup> which need not be redescribed. I have found it helpful to lubricate the tip of the pneumoperitoneum needle and the trocar with sterile glycerine, as it is a distinct aid in their passing through the tissues. When the nature of the lesion could not be determined by inspection alone, a piece of that tissue was removed for histologic study. This was necessary in about one-fourth of the cases examined.

#### CONTRAINDICATIONS

There are certain types of cases in which peritoneoscopy should not be used. These are as follows:

1. Acute abdominal inflammatory disease. Here the danger of spreading the infection is prohibitive.
2. Abdominal distention. In these cases the intestinal wall is thinned out by distention and is too vulnerable to the possibility of perforation by the advancing needle or trocar.
3. Known intra-abdominal adhesions. This type of case is not an absolute contraindication for many times by means of entering the abdomen at a site some distance from the adherent area the examination can be satisfactorily and safely carried out. It must be remembered, however, that all the known accidental perforations of the intestine have occurred in this group.

#### INDICATIONS

Peritoneoscopy should be performed only with a specific purpose in mind. It should be used to establish a differential diagnosis, to con-

## PERITONEOSCOPY\*

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PERITONEOSCOPY has attracted a good deal of attention in the recent American literature. It is a simple and relatively safe method of visualizing certain of the intraperitoneal organs or of obtaining a biopsy, if necessary, to establish a diagnosis. In selected cases it can replace the more serious procedure of an exploratory laparotomy. Whenever suitable this is a desirable substitution, for it is a minor procedure, performed under local anesthesia with a minimal risk and expense, requiring but one day's hospitalization as contrasted with the two to three weeks' hospitalization required for a laparotomy as well as its higher mortality and greater discomfort.

Peritoneoscopy is not a new procedure but originated in 1901. In that year Ott,<sup>1</sup> a Russian, inserted a speculum through a small incision in the abdominal or vaginal wall and by means of a head mirror inspected the peritoneal cavity and its contents. In the same year and independently Kelling,<sup>2</sup> in Germany, described a technique for what he termed coelioseopy. His technique was quite similar to the one now generally used and consisted of first creating a pneumoperitoneum with a small blunt needle, then inserting a Nitze cystoscope into the abdominal cavity and inspecting its contents. The method had been used only on dogs and was overlooked by the medical profession at large. In 1910 Jacobaeus,<sup>3</sup> of Stockholm, unaware of Kelling's work, published an identical procedure by which he had inspected the peritoneal cavities of 17 patients with ascites. Jacobaeus made several subsequent reports recommending the procedure, and although Kelling later recorded his use of the method in human beings, the former's name became more closely associated with laparoscopy, as he termed it. In 1911 Bernheim<sup>4</sup> at the Johns Hopkins Hospital examined the peritoneal cavity of 2 patients by means of inserting a small bore proctoscope through the abdominal wall and inspecting the various organs. He called this method organoscopy. Although successful, it was not well received and its use was abandoned.

The present interest in the subject has been aroused chiefly by the convincing work of Ruddock,<sup>5</sup> of California. He has published a large series of examinations with such success that the method has become firmly established as a diagnostic procedure. I have been able to collect the reports of over 2,000 peritoneoscopic examinations performed by twenty-two different operators. In this total series there have been 2 deaths, 1<sup>5</sup> of which was due to hemorrhage from a biopsy wound in

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TABLE I

	SHACKELFORD'S SERIES	COLLECTED FROM LITERATURE
Normal abdomen	14	72
Cirrhosis of liver	10	334
Carcinoma of ovary	8	79
Peritoneal implants	6	105
Fibroid uterus	4	47
Metastases to liver	4	167
Adhesions	4	75
Carcinoma of pancreas	4	8
Hydrops of gall bladder	4	31
Ectopic pregnancy	3	63
Normal pregnancy	3	19
Carcinoma of gall bladder	2	9
Carcinoma of rectum	2	4
Carcinoma of stomach, operable	2	83
Tuberculous peritonitis	2	52
Ovarian cyst	2	63
Peptic ulcer	1	6
P. I. D.	1	49
Failure of examination	3	
Incorrect diagnosis	2	
Total	81	

## COMPLICATIONS

There have been no deaths in my series and only 2 in the over 2,000 cases reported. In one of my cases the intestine was perforated with the trocar. It was immediately repaired by suture and no sequelae developed. Ten other such mishaps have been reported, but convalescence was uneventful in each. In 9 of these the wounded intestine was immediately sutured, but in the other, which was perforated by the pneumoperitoneum needle, the needle was simply withdrawn and no attempt at repair made.

In another of my cases subcutaneous emphysema was an annoyance for six days but subsided spontaneously. No other complications have occurred.

Biopsies were taken in about one-fourth of the cases without any harmful effects.

There were 3 failures and 2 incorrect diagnoses made. The first was the one in which the intestine was perforated and the examination was not completed. In 2 other cases dense intra-abdominal adhesions prevented carrying out the procedure. In another of my early cases in which an abdominal mass was present, I stated no metastases could be seen; however, later operation showed numerous small nodes in the omentum which the peritoneoscopist had not recognized, although they had been seen. In another instance I was again at fault in diagnosing an ovarian cyst in what turned out to be a distended loop of sigmoid caught by a band of adhesions. This illustrated the point that only those lesions which can be identified positively should receive a positive

firm a clinical impression, or to determine the presence, extensiveness, and nature of a suspected mass. It will often disappoint if used only for a general tour about the abdomen without such a specific purpose in mind.

In the usual case the greater part of the surface of the liver, the fundus of the gall bladder, the anterior wall of the stomach, colon, the surface of the omentum, and the parietal peritoneum are easily visualized with the patient supine. The spleen is not seen when normal in size unless the patient is placed on his right side, in which case its tip comes into view. If enlarged it can readily be examined in either instance. By placing the patient in the Trendelenburg position, both tubes, ovaries, fundus of the uterus, cul-de-sac of Douglas, and posterior peritoneal wall of the bladder can be examined. The appendix is only rarely observed, while the pancreas and kidneys are never seen, although a tumor of either may project or extend into the field of vision. As a result we have found the greatest use of the procedure in establishing the diagnosis of cirrhosis or malignancy, either primary or secondary, of the liver; tuberculous peritonitis; determining the operability of carcinoma of the stomach; and identifying various lesions of the female pelvic organs. It also would seem that in all cases of ascites, peritoneoscopy should be performed at the time of abdominal paracentesis, as the procedures are identical, and a positive diagnosis can be established without additional risk or discomfort.

#### RESULTS

My personal results are best seen by consulting the first column of Table I. In the second column of that same table, for the purpose of comparing experiences, are listed the number of cases reported in the literature in which the same lesion has been recognized by other operators. There have been many additional conditions identified by these authors which are not included, as the list would be too long.

A word of explanation should be made of a few of these groups. The 3 cases of normal pregnancy were individuals known to be pregnant but in whom an ectopic pregnancy was suspected. This suspicion was disproved and they went on to a normal delivery at the proper time. The carcinomas of the pancreas were not seen directly but were diagnosed by the histologic study of a biopsied malignant extension. The carcinomas of the rectum had been previously identified by local biopsy, but peritoneoscopy showed their inoperability due to the presence of metastases in the liver. The 2 cases of operable carcinoma of the stomach were in patients known to have a large filling defect in the stomach and both of whom had an easily palpable abdominal mass. In each instance the condition was considered to be clinically hopeless, but peritoneoscopy revealed no metastases to the liver or omentum, and they were both later successfully resected.



# TRANSTHORACIC, TRANSPLEURAL LIGATION OF THE FIRST PORTION OF THE LEFT SUBCLAVIAN ARTERY

## A REPORT OF THE FIRST CASE

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### INTRODUCTION

THE FIRST portion of the subclavian artery extends from the point of origin of the vessel to the inner border of the anterior scalene muscle. The right subclavian arises from the innominate artery at the level of the sternoclavicular joint. Thus, its first portion is short and relatively superficially placed. Since it often rises above the level of the inner end of the clavicle, it usually can be ligated readily through a supraclavicular approach. By contrast the left subclavian arises from the aortic arch and ascends through the superior mediastinum to the root of the neck. Its first portion thus lies deeply within the thorax. In order to ligate this portion of the vessel, the surgeon must either work at a considerable depth through a supraclavicular incision or approach the vessel more directly by removing portions of the clavicle and sternum or upper ribs.

Ligation of the first portion of the subclavian artery was first performed by Colles<sup>1</sup> in 1813. On that occasion, through a supraclavicular approach, he tied off the vessel on the *right* side in a patient suffering from traumatic subclavian aneurysm. In commenting upon his case, Colles expressed the opinion that ligation of the first portion of the *left* subclavian was impracticable because of difficulty of access and the danger of injuring the adjacent pleura, internal jugular vein, and common carotid artery. It is interesting to note that at the time, practically all contemporary British surgeons and anatomists concurred. In 1845, however, Rodgers<sup>2</sup> succeeded in ligating the first portion of the *left* subclavian and called attention to the danger of injuring the thoracic duct and the pleura during the course of the procedure. Stimulated by the surgical exploits of Colles and Rodgers, ligation of the first portion of the right and left subclavian was attempted by others; and the operation, although not performed frequently, became firmly established.

Although the early observers were proved incorrect in their assumption that ligation of the first portion of the left subclavian was impossible, the procedure nevertheless was, and still remains, difficult and hazardous. In this connection the reports collected by Halsted<sup>3</sup> of 22 such attempts made between 1845 and 1924 are significant. In only 7 of these 22 cases could the vessel be approached through a supra-

<sup>1</sup>Received for publication, Feb. 7, 1941.

diagnosis, and if in doubt, the tissue should be biopsied, or if that is undesirable, it should merely be described. No further mistaken positive diagnoses have been made.

#### PRACTICAL RESULTS

So far the discussion has centered on the academic side of medicine, concerning mainly the technique and possible diagnostic scope of the procedure. However, the method has practical value as well. By its means we have prevented the performance of what would have been 27 useless laparotomies. In addition, 10 patients in whom operation was not being considered were found to have lesions requiring surgical intervention. In the remaining 44 patients a suspected diagnosis was confirmed and the contemplated therapy carried out with the assurance gained by the removal of all doubts as to its correctness.

#### SUMMARY

1. Peritoneoscopy is a relatively safe and minor procedure.
2. Its greatest value is in diseases of the liver, pelvic organs, tuberculous peritonitis, and for the determination of the nature and extent of malignant tumors.
3. It should not be used in cases with acute inflammatory conditions, abdominal distention, or multiple adhesions.
4. It should be used only with a definite purpose in mind as to make a differential diagnosis, to confirm a suspected diagnosis, or to identify and localize a tumor.
5. By its means some patients were spared a useless laparotomy and a fewer number previously considered inoperable were found operable. In others therapy could be forced more vigorously when all doubts as to the correct diagnosis had been removed.

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ance of left pneumonectomy through the anterior approach advocated by Rienhoff.<sup>4</sup> Accordingly it was decided to employ a similar incision in the present case.

Operation was performed on Sept. 24, 1940, under cyclopropane anesthesia administered through a snugly fitting face mask. The patient was placed on her back with sand bags beneath the left hip and shoulder, and the arm was extended at a right angle in order to permit access to the axilla. A hockey-stick incision was made in the second intercostal space on the left side, with its long arm extending from the edge of the sternum to the anterior axillary line. The short arm of the incision was carried upward along the edge of the sternum to the lower border of the first rib. The second and third costal cartilages were divided close to the sternum and the internal mammary vessels ligated and divided at the upper and lower limits of the operative field. The incision in the second intercostal space was deepened down to the pleura and the latter opened freely. The second and third ribs were separated widely with the Lilienthal rib spreader and the lung permitted to collapse out of the field of vision. The aorta then was readily seen and the left subclavian artery easily could be followed upward to the summit of the chest from its point of origin on the convexity of the aortic arch. The left common carotid could not be visualized. A short, vertical incision was made in the mediastinal pleura over the lowermost portion of the subclavian and the vessel freed by blunt dissection. Two strands of heavy, braided silk next were passed beneath the vessel with a ligature carrier. Before tying these ligatures, the subclavian was compressed, and the carotid pulse was sought in the neck. After ascertaining that carotid pulsation was present, the subclavian ligatures were tied securely, the first, about one-half inch from the aorta, and the second, about one-fourth inch further distally. The incision in the mediastinal pleura was left open in order to permit the escape of fluid into the left chest. The ribs were brought together with pericostal sutures of chromic catgut and the thoracic parietes closed in layers without drainage. The lung was inflated under positive pressure by the anesthetist as the thorax was closed. Although there was bleeding from collateral vessels in the skin and muscle during operation, it presumably was much less than would have occurred had the approach been made through the conventional supraclavicular incision. The child stood the procedure well and left the operating table in good condition.

Small amounts of serosanguineous fluid were aspirated from the left chest on three occasions during the week following operation. Convalescence from the procedure otherwise was uneventful. (The further course is not relevant but the case, which was of unusual interest and ended in recovery, will be reported in a separate communication.)

#### DISCUSSION

Because of the relative infrequency of surgical conditions (chiefly hemorrhage and aneurysms) of the subclavian artery, the subject of ligation of the first portion of this vessel is perhaps of only minor interest to most surgeons. During time of war, however, it takes on new importance. Thus, experience in World War I indicates that in the present conflict, gunshot and other penetrating wounds of the subclavian vessels will be not infrequent. While in some cases hemorrhage will result in early mortality, in others the bleeding may be checked sufficiently to permit transportation of the patient to a hospital. Experience indicates further that those patients who do not succumb to massive subclavian hemorrhage usually develop large hematomas which render subsequent attempts at surgical ligation extremely difficult and hazardous. Because of these hazards (especially

clavicular approach, by dividing the soft parts alone. In the remaining 15 cases operation involved resection of the clavicle in 6, resection of the clavicle and portions of the sternum in 4, and resection of the clavicle, sternum, and first rib in 4. In the final case (Sherrill<sup>6</sup>) the vessel was approached extrapleurally through a posterior thoracic incision with resection of the second, third, and fourth ribs. It is important to point out that ligation of the first portion of the left subclavian is difficult not only because the vessel is situated largely within the thorax, but also because the procedure at times is complicated by abnormalities referable to the condition for which ligation is performed. In the cases collected by Halsted, ligation was necessitated by an aneurysm of the subclavian artery in all but one. (In the latter, the lesion was a malignant tumor which occupied the supraclavicular fossa.) In the presence of an aneurysm, ligation of the subclavian is apt to be attended with serious hemorrhage as the result of accidental injury of the aneurysm itself and from numerous adjacent collateral vessels which must be traversed during the course of operation. Other complications, reported in the cases collected by Halsted, include operative shock, injury to the thoracic duct, brachial plexus and pleura, and hemorrhage (sometimes fatal) from adjacent large vessels, such as the left common carotid artery, left internal jugular vein, and left innominate vein. Additional objectionable features of operation are that it (1) is usually time-consuming, and (2) is apt to be followed by appreciable deformity if the removal of substantial portions of bone is necessary. Thus the conventional method of ligation presents a number of serious disadvantages and dangers.

#### CASE REPORT

Recently the author was confronted with a case of diffuse, congenital arteriovenous aneurysm involving the left upper extremity in a child 13 years of age. Operation had been advised because of increasing cardiac insufficiency. The procedures which previously had been performed consisted of double ligation of the axillary artery and vein, excision of an axillary arteriovenous communication, and an attempt at ligation of the third portion of the subclavian artery. Because of profuse hemorrhage from numerous collateral vascular channels which involved the entire supraclavicular region and root of the neck, it had been necessary to discontinue the last operative procedure before the vessel was exposed. In view of this bleeding it seemed fair to assume that further attempts to ligate any portion of the subclavian through the conventional surgical approach again would be attended by ominous hemorrhage. Accordingly, the only safe method appeared to be to approach the vessel at some distance from the area in which collateral circulation existed. It seemed that this could be accomplished most readily by exposing its first portion through a transthoracic, transpleural incision made at some distance from the previous operative site. Although the merits of such a surgical approach appeared obvious, a search of the literature failed to disclose any reference to its use in subclavian ligation. In operating upon cases of patent ductus arteriosus, the author previously had employed the anterior, transthoracic, transpleural incision advocated by Gross,<sup>2</sup> and had been impressed with the excellent exposure of the left subclavian as it took origin from the aortic arch. This also was noted during the perform-

In view of the fact that operation upon the innominate artery, and at times upon the proximal portion of the right subclavian artery, presents difficulties and dangers similar to those encountered in exposing the left subclavian, ligation of the innominate artery through a transthoracic, transpleural approach carried out on the right side might be attempted in certain cases.

The incision described also appears to afford the best approach for direct surgical attack upon an aneurysm involving the very first portion of the left subclavian or innominate artery.

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uncontrollable hemorrhage) many surgeons during World War I deemed it wise never to operate upon such patients. The result was that many of the latter subsequently succumbed either of infection or secondary (infective) hemorrhage; or, if sufficiently fortunate to survive, developed an arterial or arteriovenous aneurysm.

The method of ligation herein described appears to be well suited to the treatment of certain wounds of the subclavian vessels, for it permits rapid exposure and ligation of the vessel in an area far removed from the site of injury. Once hemorrhage has been controlled, the local site of injury can be explored and débrided freely. In cases in which there is evidence that injury to the subclavian vessels is complicated by adjacent intrathoracic trauma, the procedure has the added advantage of permitting direct visualization and an attempt at treatment of the intrathoracic component of the wound.

In cases of injury of the right subclavian artery, when exposure of the vessel through the conventional approach is difficult or unsafe, or in cases of injury of the innominate artery, a right-sided transthoracic transpleural approach might be attempted for ligation of the innominate artery.

In certain cases of traumatic aneurysm of the first or second portion of the subclavian artery, the methods of subclavian and innominate ligation which have been described may result in cure alone or may be employed as a preliminary to subsequent excision or distal ligation. Likewise in the rare case of nontraumatic aneurysm of the very first portion of the left subclavian or innominate artery, the transthoracic, transpleural approach appears to afford a good exposure for direct surgical attack (either ligation or excision) upon the lesion.

#### SUMMARY AND CONCLUSIONS

1. The case herein reported appears to represent the first attempt at transthoracic, transpleural ligation of the first portion of the left subclavian artery to be recorded in the literature.

2. This approach to the first portion of the left subclavian artery permits rapid and free exposure of the vessel proximal to its branches.

The experience of surgeons who have operated upon cases of patent ductus arteriosus through such an approach has already demonstrated that it is not attended with appreciable shock (even in debilitated children suffering from cardiac insufficiency).

Removal of portions of the clavicle, sternum, and ribs is not necessary. The exposure, therefore, is not apt to be time-consuming nor followed by deformity.

There is no danger of injury to the thoracic duct, brachial plexus, or adjacent large vessels at the root of the neck.

The procedure is recommended in cases in which ligation of the first portion of the left subclavian is necessary alone or in combination with another procedure, or as a preliminary procedure.

In view of the fact that operation upon the innominate artery, and at times upon the proximal portion of the right subclavian artery, presents difficulties and dangers similar to those encountered in exposing the left subclavian, ligation of the innominate artery through a transthoracic, transpleural approach carried out on the right side might be attempted in certain cases.

The incision described also appears to afford the best approach for direct surgical attack upon an aneurysm involving the very first portion of the left subclavian or innominate artery.

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## RECURRENCES AND FAILURES FOLLOWING THE MODERN TREATMENT OF VARICOSE VEINS

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NOTWITHSTANDING the important improvements made in the modern treatment of varicose veins, recurrences and failures occurred in almost 16 per cent of the patients treated by us from January, 1935, to January, 1940. Recurrences were greater in my own service nine years preceding that period. The recognition of the absolute necessity of ligating the saphenous vein when there was incompetency of the saphenofemoral valve was alone responsible for a reduction in the percentage of recurrences in our early work.

We recognize that even with the most careful treatment there is a certain tendency toward recurrence in some patients and also a tendency to develop a new group of varicosities. So far we have been unable to prevent re-formation of varicosities in these patients. Even considering all these factors, I believe the percentage of recurrences could be minimized by careful, critical studies.

For this presentation I have reviewed 230 patients with recurrences and failures who were treated by me or under my direct supervision. The patients who were treated elsewhere, but who consulted us for further treatment of recurrences, were purposely excluded.

For simplification of our study these patients were classified in two groups: (a) those who had only injection of sclerosing solutions, and (b) those who had ligation followed by oblitative treatment.

Ninety-eight patients belonging to this first group were studied.

The record shows that 33 patients who were diagnosed as having simple dilatation of the superficial veins and who were successfully treated with sclerosing solution returned one to five years afterward with recurrences. Examination revealed that they all had developed incompetency of the saphenofemoral valve during this interim. High ligation and further oblitative treatment were advised.

Eighteen patients were previously diagnosed as belonging to the Trendelenburg positive group and ligation was advised. They refused operation and were treated by injection. Fifteen of these patients showed a fair obliteration after injection, but canalization developed within a very short time. Fourteen patients of this latter group were eventually ligated and benefited. For the last three years we have made it a rule not to give injection treatment as a palliative measure if ligation is refused.



In 9 patients a correct diagnosis was undoubtedly missed, and they were treated by injection when ligation should have been performed as a preliminary step. Careful examination is necessary to determine the patency of the saphenofemoral valve in obese individuals where the saphenous vein may be buried deeply in fatty tissues. Trendelenburg and Schwartz tests may have to be repeated and correctly interpreted. Sometimes it will be necessary to palpate the saphenous in various locations of the thigh with the patient in different positions. In 3 patients the high ligation had to be supplemented by a ligation in a lower level of the thigh because of incompetency of the valve of the intercommunicating vein. This was demonstrated by the comparative tourniquet test.

One patient belonged to the Trendelenburg double positive group. Multiple ligations and injection treatment produced unsatisfactory results.

The remaining 34 patients showed a tendency to recurrence and reformation of superficial varicosities without any disturbance of the normal venous flow. These were treated periodically with sclerosing solution.

I have reviewed 132 patients of the second group who had recurrences following some form of ligation operation. High ligation in the saphenofemoral junction has been our operation of choice for many years. In earlier work, a few technically difficult cases were ligated in the upper third or middle of the thigh. The incision in the groin was also avoided in some obese individuals because of the presence of moist eczema. Seventeen such patients had recurrences and required high ligation.

I have discontinued performing ligation as a primary operation in the lower level. Experience has proved that the result in low ligation is unsatisfactory.

Since the publication of Edwards' important paper in 1934<sup>1</sup> regarding the anatomical pattern of the saphenous vein, many articles have appeared in the literature regarding the reformation of venous channels through the uppermost tributaries of the saphenous. I have operated upon a few patients with recurrence of this type who had had their original operation elsewhere. In my own group I have encountered only 2 such cases. Both had had high saphenous ligations and were discharged after a satisfactory course of obliterative treatments. When next seen they were pregnant and suffering from marked varicosity of the labia. A few months after the termination of pregnancy one of these patients was reoperated upon, and with a great deal of difficulty I isolated a patent pudendal branch which had been missed during the original ligation. The second patient was successfully treated with only injection of sclerosing solution without further recurrence. Solomons<sup>2</sup> suggested injecting these pudendal varicosities during pregnancy with quinine and urethane. I have never had the courage to follow his suggestion. The patients I have seen with pudendal

varicosity during pregnancy almost always had an incompetent saphenofemoral valve complicating the condition, so I have advised them to wait for treatment until the termination of pregnancy.

The abnormal pattern of the uppermost part of the saphenous vein is common, and we have encountered a full share of various abnormalities. I have taken painstaking care to ligate any of the uppermost tributaries present. This is done routinely whenever the external pudendal, superficial circumflex, iliac, and superficial epigastric veins empty into the upper end of the saphenous vein instead of into the femoral vein. The accessory veins, lateral or medial femoral, are in the great majority of patients located too far distally to expose during high ligation. In some instances one of them may be located quite high and anterior to the saphenous and may be ligated by mistake as the saphenous vein. This was undoubtedly the cause of recurrence in a few patients I have exposed who had been operated upon elsewhere. Since we began routine peripheral injection of sclerosing solutions in the severed distal portion of the saphenous during ligation, we have encountered very few patent accessory femoral veins as the cause of recurrences. In the majority of patients this injection obliterates these accessory veins. In 6 instances it was found that patency of the accessory vein was the cause of recurrence. The lateral femoral vein was ligated and injected in 2 cases; by subsequent experience it was determined that by injection alone satisfactory obliteration could be obtained.

We have had limited experience in the past with the old stripping and excision operation. A few patients with recurrence and failure after such operation elsewhere responded satisfactorily to ligation and injection treatment in our service. We have also operated successfully upon 5 patients who have had the Schede type of operation elsewhere with failures.

Varicosities of the lesser saphenous almost always are caused by the pressure transmitted through communications with the long saphenous. In some of my earlier patients I ligated and excised the communicating vein just medially and behind the knee as a special precaution in addition to the high ligation. This additional step is very seldom necessary. High ligation of the saphenous and obliteration of the small saphenous alone will prove sufficient in the majority of patients. If the lesser saphenous is greatly dilated, it may have to be ligated in the popliteal space as described in previous publications.<sup>3</sup>

It has been my custom to remove a segment of the saphenous vein during ligation. Undoubtedly in some instances this procedure was not adhered to. I have never seen recurrences caused by reestablishment of ligated and cut ends. I have my honest doubts in this matter. In several instances during reoperation on patients operated upon elsewhere, a patent saphenous was found. This, I believe, was either missed during the original operation or ligated but not cut.

The great majority of recurrences in the ligated group in my own service occurred when there was not only an incompetency of the saphenofemoral valve but also of the one or more valves of the veins communicating between the deep and superficial systems of the thigh. Although familiar with this complication, it was not always possible to diagnose it or to differentiate it from the Trendelenburg double positive group.

To Ochsner and Mahorner<sup>4</sup> the credit is due for describing the comparative tourniquet test by which incompetency of the communicating veins in the thigh can be accurately demonstrated. They have also made it clear that this incompetency in the majority of patients is only limited to the thigh and fortunately does not extend below the knee. It can be easily understood that the normal flow of blood in the venous system of the lower extremities is from superficial to deep. But when incompetency of the valves of the intercommunicating veins is present, the blood flow is reversed from the deep to the superficial. Ninety-two patients with recurrences following high ligation required further ligation in one, two, or three lower levels in the thigh to produce a satisfactory result. These levels were determined by the simple comparative tourniquet test. In going over the record of these patients I found that in some the condition was not properly recognized, while in others it was not properly differentiated from the Trendelenburg double positive group. We also found another incipient group where the back flow through the saphenofemoral junction could be easily demonstrated, but the lower level of the leaks between the superficial and deep venous system could not be clearly determined until some time after high ligation was performed. For the last four years we have been performing the high and low ligations in one sitting in all indicated cases. I am convinced that this important step has helped in reducing the number of recurrences.

The remaining 15 unsuccessful cases belonged in the Trendelenburg double positive group and showed not only incompetency of the saphenofemoral junction and of the intercommunicating veins of the thigh, but also incompetency of the veins of the intercommunicating system in the calf and lower leg. Multiple ligations, excision, and segmental obliteration were performed. Though the immediate result proved satisfactory, the final follow-up was far from encouraging. Linton's<sup>5</sup> operation for the ligation of communicating veins in the lower leg may offer some hope to the patients who present multiplicity of symptoms caused by venous stasis. My own experience is limited to 2 such cases, and it is too early to draw any conclusions. This operation is of great magnitude and cannot be used as a routine measure. Uncomplicated cases belonging to this group could be made comfortable with a properly fitted elastic stocking or bandage. Fortunately, less than 2 per cent of varicose vein patients seen by us belonged to the Trendelenburg double positive group.

## CONCLUSIONS

1. When there is dilatation of superficial veins of the lower extremity without disturbance of the normal flow of the venous blood, adequate injection of sclerosing solution will prove satisfactory in the majority of patients.

2. If backflow of blood through an incompetent valve in the saphenofemoral junction is present, a high ligation and sectioning of saphenous followed by obliteration of varicosities will prove sufficient. Ligation of the uppermost tributaries of the saphenous when present and peripheral injection of the severed distal portion are valuable steps in the ligation operation.

3. Incompetency of one or more valves of the communicating veins of the thigh between the superficial and deep venous systems requires additional ligation in the lower level.

4. Multiple ligation, excision, and segmental obliteration in patients with incompetency of the valves of the communicating veins of the whole lower extremity including the calf and lower leg have not produced permanently satisfactory results. Linton's operation may offer hope in some patients. Uncomplicated cases can be made comfortable with elastic bandages.

5. Notwithstanding what method of treatment is used, there is a tendency in some patients to recurrence and re-formation of varicose veins. Observation of patients at regular intervals and critical investigation of the causes of recurrence and institution of proper treatment will decrease the number of failures.

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## BLOOD ETHER LEVELS IN SURGICAL ANESTHESIA

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SINCE the first use of ether as a human anesthetic agent by Long in 1842, many determinations have been made in animals and a few in man to ascertain anesthetic and lethal levels. The problem has been approached mainly in two ways: (1) by measuring the ether vapor concentration in air, either as administered for anesthesia or as the alveolar tension when exhaled, and (2) by measuring the ether concentration in blood samples taken during anesthesia.

Probably the first determination of ether concentration in the anesthetic state was made in 1847 by Lassaigue,<sup>1</sup> who measured the ether in the venous blood of a dog. Since that time various workers including Snow,<sup>2</sup> Bert,<sup>3</sup> Madelung,<sup>4</sup> Stange,<sup>5</sup> Shaffer and Ronzoni,<sup>6</sup> Ronzoni,<sup>7</sup> Haggard,<sup>8</sup> Robbins,<sup>9</sup> and Calderone<sup>10</sup> have made determinations in animals by air analysis. Among those who have carried out ether determinations on blood samples from animals are Lassaigue,<sup>1</sup> Nieloux,<sup>11</sup> van Leeuwen,<sup>12</sup> Shaffer and Ronzoni,<sup>6</sup> Ronzoni,<sup>7</sup> Haggard,<sup>13</sup> Karber,<sup>14</sup> Robbins,<sup>9</sup> Calderone.<sup>10</sup> Determinations made by air analysis on human beings include those of Dreser,<sup>15</sup> Connell,<sup>16</sup> Boothby and Sandiford.<sup>17</sup> Direct determination of the concentration of ether in the blood of anesthetized human beings has been made by Gramen,<sup>18</sup> White,<sup>19</sup> Webb,<sup>20</sup> and Koller.<sup>21</sup> The interest of the workers cited above was variously distributed between anesthetic and lethal levels, distribution ratios, recovery curves, absorption and excretion, and possible synergism with other drugs.

The criteria for "surgical anesthesia" varied with the different workers. Muscular relaxation, loss of pain response, alteration of corneal or deep reflexes, character of respiration, etc., were considered among the criteria. However, in dogs at surgical anesthesia the results of Nieloux<sup>11</sup> (105 to 110 mg. per cent), of Haggard<sup>13</sup> (80 to 91 mg. per cent), of Robbins<sup>9</sup> (90 to 113 mg. per cent), and of Calderone<sup>10</sup> (81 to 95 mg. per cent), show good agreement and range only from 80 to 113 mg. per cent. Ronzoni<sup>7</sup> and van Leeuwen,<sup>12</sup> working with dogs and cats respectively, made more definite attempts to correlate anesthetic level with stage by determining loss of reflexes in response to electrical stimulation of nerve trunks.

Of more interest to us are the results in human beings. Gramen<sup>18</sup> made 700 determinations on 52 patients including expired air, urine, milk, and also venous blood, drawn at various times during or following operation. His monograph contains an excellent review of the literature on ether determinations. He considered five clinical stages of anesthesia with Stages III and IV being in the range of customary surgical anesthesia. He differentiated between Stages III and IV on

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the basis of pain reflexes from the operative field. For Stage IV, or deep surgical anesthesia, his results on 67 determinations ranged from 41 to 111 mg. per cent with an average of 80 mg. per cent. Koller<sup>21</sup> in 51 patients found a range of from 30 to 100 mg. per cent sufficient for surgical anesthesia. White<sup>19</sup> during de-etherization of 12 patients found that surgical anesthesia ranged from 100 to 150 mg. per cent while light surgical anesthesia varied from 70 to 100 mg. per cent.

There is apparent disagreement among the various workers as to the effect of morphine or morphine-scopolamine or other premedicant drugs on the blood ether levels required for surgical anesthesia. Madelung<sup>4</sup> found that one-half to two-thirds of the usual concentration of the anesthetic agent in the alveolar air of rabbits and dogs was sufficient for surgical anesthesia when morphine and scopolamine were given preoperatively.

Stange<sup>5</sup> reported that morphine lessened by one-third the concentration of ether necessary for light anesthesia in rabbits but did not lessen the dosage for deep anesthesia or respiratory failure, unless excessive doses of morphine were given. Calderone,<sup>10</sup> working with dogs, found that 2 to 5 mg. per kilogram of morphine did not lessen the concentration of ether in the blood necessary for either surgical anesthesia or respiratory failure. Barlow and Stormont<sup>22</sup> found that in rats, opium alkaloids are additive to nitrous oxide. Webb<sup>20</sup> found in human beings that venous blood following morphine 0.010 Gm. and atropine 0.0004 Gm. contained 41 to 110 mg. per cent of ether during light surgical anesthesia, and 110 to 170 mg. per cent during deep surgical anesthesia. Following an unstated amount of morphine and hyosine he found blood ether levels ranging between 39 and 100 mg. per cent sufficient for abdominal operations.

In the above reports it should be noted that there is considerable difference in the amounts of the drugs employed. Stange and Madelung administered in rabbits 20 mg. per kilogram of morphine and 10 mg. per kilogram of morphine and of scopolamine respectively, while Calderone<sup>10</sup> used 2 to 5 mg. per kilogram of morphine in dogs.

It is the general belief among many surgeons and anesthetists that the preoperative administration of morphine alone or in combination with atropine or hyosine materially reduces the amount of ether required to produce surgical anesthesia and shortens the induction time, in addition to quieting the unrest of the patient in anticipation of the operation and providing some analgesia immediately postoperatively. It is probable that this concept has developed from clinical observation and does not represent controlled investigation.

In this study we have attempted to evaluate the effect of morphine alone, or in combination with hyosine or atropine on ether levels in surgical anesthesia. With a simple, rapid method for determining blood ether concentration at our disposal,<sup>21</sup> determinations were made on patients using various methods of administration of ether anesthesia both with and without premedication. Special emphasis was placed

on bringing the patients to the same level of anesthesia as determined by the clinical signs described by Guedel.<sup>24</sup> The various groups were compared in an attempt to evaluate the effect of premedication on the concentration of ether in the blood.

#### ANESTHETIC METHODS AND PREMEDICATION

Consecutive patients receiving ether anesthesia were used in this study. They included neurosurgical, upper and lower abdominal, plastic and tonsil cases. The ages varied from 5 to 70 years.

Premedication consisted of morphine alone, morphine-atropine, or morphine-hyoscine, and codeine in the case of young children. These drugs were administered in the usual clinical doses of 0.010 to 0.015 Gm. of morphine, and 0.0003 to 0.0004 Gm. of atropine or hyoscine. Codeine ranged from 0.02 to 0.03 Gm. In every case the premedication was administered twenty to forty-five minutes before the induction of the anesthetic. A small series received avertin as basal anesthetic, and some patients received no premedication.

Four different anesthetic methods were employed: (1) induction and maintenance with open-drop ether on a Schimmelbusch face mask, designated as "drop alone"; (2) short semiopen induction with nitrous oxide-oxygen for two to five minutes, followed by open-drop ether on a Schimmelbusch face mask, designated as "nitrous oxide-oxygen to drop"; (3) short semiopen induction with nitrous oxide-oxygen followed by a closed system with ether dropping in a rebreathing bag; there was maintenance flow of oxygen, and soda lime absorption of carbon dioxide, designated as "closed metric"; (4) semiopen induction with nitrous oxide-oxygen, followed by constant flow of nitrous oxide and oxygen over ether, designated as a "semiopen  $N_2O-O_2$  constant flow with ether." Ethylene could not be used as an induction agent as it appeared in the blood samples, and was found to be present, although not quantitatively, in the analysis.

#### ANESTHETIC LEVEL AND THE BLOOD SAMPLE

The selection of a standard level of anesthesia in an assay such as this is extremely difficult. So-called "surgical anesthesia" will show a wide range of variability. Ronzoni<sup>7</sup> suggested also that the length of time under anesthesia is a factor in the amount of ether required. Gramen<sup>18</sup> used the abolition of pain in human beings as the criterion but showed that this varied between cutaneous, muscular, and peritoneal stimulation. Others have employed electrical stimulation of nerves and reflexes in an attempt to set levels of anesthesia.

In this work we attempted to use the signs regularly employed in anesthesia, both because they represented a convenient and commonly accepted method and because of the greater familiarity of the anesthesiologists with these signs. Muscular relaxation, character of respiration, eye signs, and absence of superficial reflexes, as defined by Guedel,<sup>24</sup> were employed as criteria of the depth of anesthesia. All blood samples were drawn at the second plane of the third or surgical

stage of anesthesia. These were taken after the induction and before the operation was begun and after careful selection of the anesthetic stage by one of three experienced anesthetists. The subsequent course of the anesthetic was checked, and in cases where it was apparent that the stage had been incorrectly designated, the samples were rejected.

Single samples of blood were collected in 2 c.c. precision syringes which were found to have an error of only 0.5 to 2 per cent. Occasionally duplicate samples were run and the results were always within the limit of error of the technique. The blood samples were analyzed for ether content by a modified dichromate-sulfuric acid method recently described by some of us.<sup>23</sup> With this technique 97 to 101 per cent of ether was recovered from standard solutions of water and of blood containing ether.

The blood was necessarily drawn from the venous system, the large veins of the arm being employed. It is evident that heart, arterial, or internal jugular puncture is barred as a routine for patients. Haggard<sup>13</sup> aptly points out that unless the organism is at equilibrium or in the process of elimination of ether with moderate breathing, a venous sample from the extremity is not indicative of ether saturation for purposes of determining physiologic response. However, because the samples were always taken under comparable conditions, after smooth inductions and at apparently the same stage of anesthesia, and because the ether administration was stopped during the time of determination of the stage and drawing of the sample, it is fair to state that the samples are of clinical value, and if not representing a state of equilibrium, at least are close to it.

To check the accuracy of this contention, two blood samples were taken from each of 10 patients that were examined in the following manner. The first blood sample was drawn at the second plane of the third stage. The anesthetic was then deepened to the early fourth stage and stopped, allowing the patient to return to the second plane of the third stage by de-etherization. At this time a second blood sample was drawn. The data from this study appear in Table I. It is interesting to observe that the variation is about equal on either side, and that the second sample was slightly higher in 4 cases and slightly lower in 6 cases. It is obvious that this process of prolonged de-etherization from deep anesthesia cannot be employed routinely in human subjects for a large series of cases.

#### RESULTS

Simple averages do not show as much as graphic presentation, and the best method of analysis is statistical comparison as employed in biologic drug assays. Our data were submitted to a competent statistician\* for statistical analysis by the method of Fisher.<sup>22</sup>

For purposes of analysis the data were considered (1) under the different categories as determined by various methods of anesthesia

\*We are indebted to Dr. Bert Vos for the statistical analysis presented.



TABLE I

CASE NO.	BEFORE DEEP SATURATION (MG. %)	AFTER DEEP SATURATION (MG. %)
1	61	70
7	65	75
9	75	85
10	75	84
2	69	49
3	71	70
4	88	82
5	113	86
6	113	73
8	101	95

and various combinations of premedication used, and (2) under the combined groupings with and without premedication. The amount of ether used, the time consumed by the induction, the simple averages of blood ether levels, and the ranges covered in each category appear in Table II. In collecting the data for "combined" comparison, only the anesthetic methods of "drop alone," "nitrous oxide-oxygen to drop," and "closed metric" could be used, since the effect of nitrous oxide was in force in "semiopen nitrous oxide-oxygen constant flow with ether" as the ether levels of this category indicate. As far as the effect of nitrous oxide used only for early induction is concerned, this nitrous oxide was probably in greater part eliminated from the system during the subsequent period of ether administration. Kemp<sup>28</sup> cites a single instance where the nitrous-oxide level in the venous blood of a dog fell from over 20 per cent, an anesthetic level, to 6.9 per cent in

TABLE II

	AMOUNT ETHER USED (AVERAGE)	TIME (AVERAGE) (MIN.)	AVERAGE (MG. %)	LIMITS (MG. %)	NO. OF CASES
Drop alone					
No premedication	3.3 oz.	12	93	61-117	34
After morphine	4	16	113	73-136	9
Nitrous oxide-oxygen to drop					
No premedication	4 oz.	12	93	62-130	44
After morphine	5	13	95	77-149	10
Closed metric					
No premedication	27 c.c.	12	90	59-129	26
After morphine-hyoscine	33	13	87	52-131	25
After morphine-atropine	29	13	89	75-116	6
After morphine alone	26	14	89	52-127	15
Combined after premedication	29.6	13.7	88	52-131	46
Semiopen nitrous oxide-oxygen constant flow with ether					
No premedication	2 oz.	17	59	25-103	14
After premedication	2	14	70	26-131	18
Combined comparison: drop alone, nitrous oxide-oxygen to drop, and closed metric					
No premedication			92	59-130	104
After premedication			92	52-149	65

less than two minutes. It is a common clinical observation that recovery of consciousness from nitrous oxide-oxygen anesthesia takes place almost immediately after the anesthetic is discontinued. In substantiation of this belief we note that graphic comparison of the "drop

*N<sub>2</sub>O TO DROP AND DROP ALONE  
WITHOUT PREMEDICATION.*

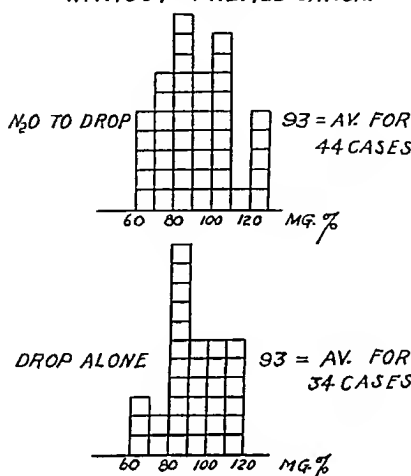


Fig. 1.

*CLOSED METRIC MACHINE.*

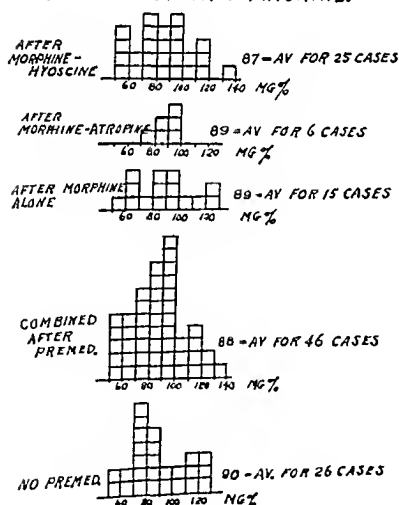


Fig. 2.

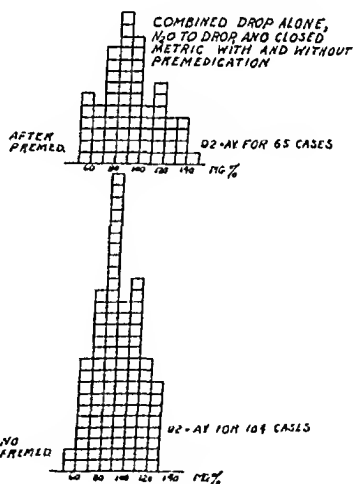


Fig. 3.

alone" and "nitrous oxide-oxygen to drop" both without premedication show similar distribution (Fig. 1) and by statistical analysis by Fisher's method shows no significant difference between the series ( $P = 0.8$ ).

The graphical presentation of the various types of premedication with the "closed metric" method of anesthesia appears in Fig. 2.

Statistical study of the "closed metric" method, comparing 26 cases with no premedication with (a) 25 cases with morphine-hyoscine and (b) 46 combined cases with premedication, gives  $P$  values of 0.5 and 0.9 respectively which represent no significant differences between the series compared. Fig. 3 is a graphic representation of the results in the combined categories of "drop alone," "nitrous oxide-oxygen to drop," and "closed metric," comparing those with and those without premedication. The statistical comparison of the combined groups gives  $P = 0.1$ , which indicates no significant difference between the series.\*

It should be mentioned that 6 cases were run with avertin as a basal anesthetic supplemented with drop ether. Eighty to 95 mg. per kilogram of avertin were used, and an average of three to four ounces of ether, the average time of induction being twelve minutes. The blood ether levels showed widespread variations; i.e., 60, 70, 60, 110, 125, and 28 mg. per cent for the 6 cases.

#### COMMENT

In evaluating data of this type, the limitations of the method must be kept clearly in mind. An investigative problem such as this is greatly complicated by the difficulties in the clinical determination of the anesthetic stage, the individual variation in reaction to the premedication and the anesthetic agent, and the variations in the general condition of patients encountered in routine surgery. Thus a large series must be studied the better to evaluate these variables.

From this series a number of observations may be made. The premedication used had little effect on the time required for the production of surgical anesthesia or on the amount of ether used. Certainly the medication did not markedly shorten the induction period; in fact, there was a slight increase in the induction time which is in agreement with Flagg,<sup>28</sup> who stated that morphine and atropine as preliminary medication prolong the induction with the open method. It is apparent from Fig. 3 that there was a wider divergence in blood ether levels in the presence of premedication. This is probably due in part to the obscuring of some of the anesthetic signs, since more difficulty was experienced in determining exactly the anesthetic stage after premedication. It is interesting to note that Gwathmey<sup>29</sup> states that the administration of morphine and scopolamine before colonic ether-oil makes the pupillary signs of little value.

From these results it is apparent that by our method there is no observable difference in blood ether levels between the groups receiving morphine, morphine-atropine, or morphine-hyoscine and the groups receiving no premedication. This observation is apparently at variance with the results of Madelung and Stange in their work with rabbits and of Webb in determinations on human beings. Although it is difficult to

\*The combined categories were analyzed by the method of Yates and Brandt as given by Snedecor.<sup>27</sup>

translate quantitatively the effect of depressant drugs from rabbits to human beings, it is probable that the amounts employed by Madelung and Stange of 10 and 20 mg. per kilogram of morphine are much greater than the usual dosages employed in human beings. Our observations are in accord with those of Calderone who found that dosages of 2 to 5 mg. per kilogram of morphine had no effect on the ether levels required for surgical anesthesia.

It is interesting to note that our series falls in fair approximation with other determinations of surgical anesthesia. The limits ranging from 59 to 139 mg. per cent, with an average of 92 mg. per cent, is about 12 mg. per cent above that of Gramen who had a large and carefully controlled series and whose stage designated as Stage IV loosely approximated our standard level. It is difficult, however, to compare series in which varying criteria were selected for determination of anesthetic level.

In conclusion we wish to state that this work has been an attempt to determine if the preanesthetic use of morphine, morphine-atropine, or morphine-hyoscine in the usual clinical doses affects the blood ether concentration necessary to produce surgical anesthesia. We do not wish, however, to discredit the use of these and other kinds of premedication, as they have a very definite selective use in preoperative preparation. Their role in decreasing apprehension, their synergistic action with gas anesthesia making it possible in indicated cases to avoid the use of ether, makes them very valuable adjuncts to anesthesia.

#### SUMMARY

1. The results of blood ether determinations on 207 clinical patients with various methods of anesthesia, with or without premedication, are presented.

2. Comparison by graphic and statistical methods reveals that patients without premedication, or with commonly used premedication, show no significant variation in blood ether levels at the second plane of third stage anesthesia.

3. Morphine in the dosages commonly employed does not appreciably decrease the time of, nor increase the ease of, induction with ether and often obscures the signs of anesthesia so that frequently higher ether levels are found after its use.

4. Blood ether levels without premedication at the second plane of the third stage of anesthesia vary from 50 to 130 mg. per cent, the greatest number falling between 80 and 100 mg. per cent.

We wish to thank Dr. T. E. Friedemann, Dr. B. F. Vos, Dr. Vermeylen, and Mr. L. Hrdina, as well as the members of the . . . . . for their assistance in this study. We also wish to express our . . . . . operation given us by the surgeons who made this investigation . . . . .

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# A COMPLICATION FROM THE USE OF GLOVE POWDER

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Union University, and the Albany Hospital)

**N**ODULES in operative scars sometimes present interesting problems in diagnosis. Commonly, they are due to malignant implants or metastases or to foreign bodies, such as suture material and cotton threads. In some cases tuberculosis and endometriosis are found. In this communication we wish to call attention to the importance of talcum powder as a causative agent not only of nodules in the skin and subcutaneous tissue of abdominal incisions, but also of tubercle-like lesions on the peritoneum. During the last year we have seen several cases in which talcum powder was responsible for the development of these lesions. Not infrequently the nodules it produces are tender to palpation and may even be painful. In the cases which we have observed, small nodules consisting of miliary granulomatous lesions resembling tubercles have been found in old abdominal incisions in 3 cases and on the peritoneal surface in 2 cases in which multiple abdominal operations had been performed. A brief report of 4 typical cases with the pathologic findings follows.

## CASE REPORTS

**CASE 1.**—A negress, 51 years of age, presented herself at the Outpatient Department of the Albany Hospital with the complaint of pain in the region of an old operative scar in the low midline of her abdomen which had been present for one week. Five years before she had had an abdominal hysterectomy and bilateral salpingo oophorectomy for multiple leiomyomas. Examination of the old incision revealed a hard, immobile, tender mass approximately 2.5 cm. by 4 cm. in size. The blood Wassermann reaction was four plus. A tuberculin test was read as two plus. There was evidence of healed primary tuberculosis on roentgenologic examination of the chest. Biopsy of the lesion was taken. Grossly the tissue appeared yellowish white in color and was firm to palpation. Microscopically many small discrete and conglomerate foreign body granulomas showing a central framework of epithelioid cells, a surrounding zone of multinucleated giant cells and lymphocytes, and a peripheral fibrous tissue reaction were seen. The lesions were considered to be miliary tubercles in the scar tissue of the abdominal wall. Examination of the tissue under the microscope with polarized light was suggested after our attention was called to the work of Freudberg<sup>1</sup> on the subject of talcum granuloma. Fig. 1A is a photomicrograph of the tissue removed from the abdominal incision of this patient. Typical miliary tubercles can be seen in the section. Fig. 1B is a photomicrograph of the same area taken after polarization of the light to demonstrate the talcum. The crystalline deposits can be seen in the foreign body giant cells.

**CASE 2.**—The second case is one in which tubercles of talcum powder origin were found on the peritoneal surface of the ileum removed from a 23 year old man with regional ileitis. Before resection of the ileum and right colon was performed, two previous operations had been done. He had first been operated upon elsewhere for

what seemed to be acute appendicitis. He had also had an ileocolostomy performed at the Albany Hospital as a first stage operation preliminary to resection. Microscopic examination of the peritoneal surface of the ileum revealed multiple tubercles, which upon examination under polarized light, proved to contain crystals which were undoubtedly talcum powder. In Fig. 2A and B an area from the markedly thickened serosa of the ileum is shown. In Fig. 2B the crystalline deposits are visible under polarized light.

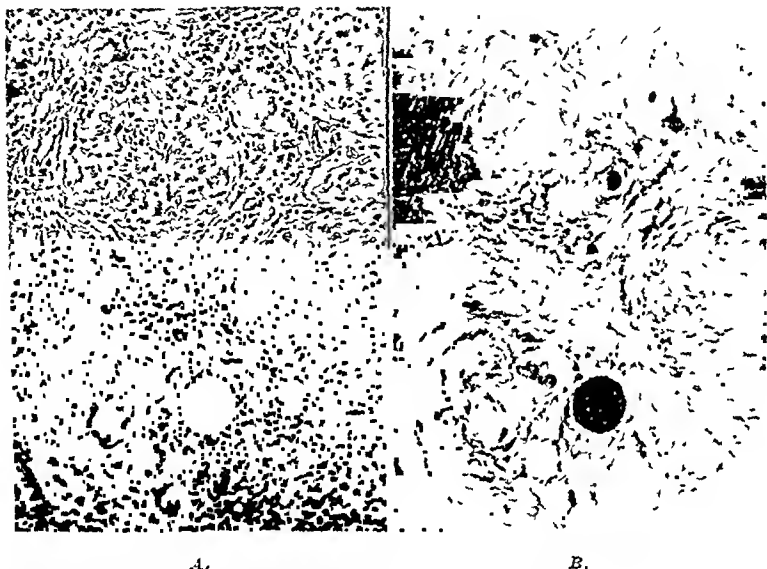


Fig. 1A —Photomicrograph of foreign body giant cells containing talc crystals in tissue removed from abdominal scar in Case 1. B, Same section as shown in A photographed after polarization of light.

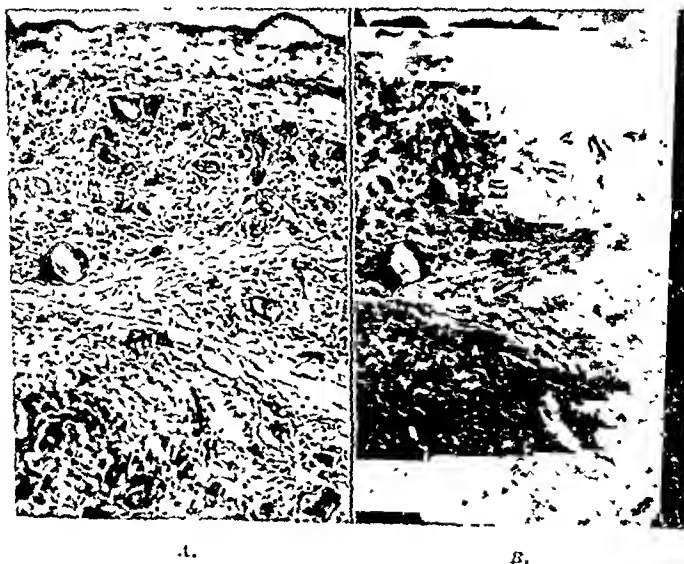


Fig. 2A —Photomicrograph of crystals of talc and foreign body giant cells on serosal surface of ileum in case of Mehlis (Case 2). B, Same as shown in A photographed with polarized light.

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**CASE 2.**—The second case is one in which tubercles of talcum powder origin were found on the peritoneal surface of the ileum removed from a 23 year old man with regional ileitis. Before resection of the ileum and right colon was performed, two regional ileitis had been done. He had not been operated upon elsewhere for



mental evidence would seem to indicate that the tissue reaction to talc is due to a chemical irritation.<sup>1</sup> That the reaction to lycopodium may also be due to a chemical factor is pointed out by Erb,<sup>2</sup> who calls attention to the fact that the spores are acid-fast just as are tubercle bacilli and that the lesions produced are almost identical.

Fienberg has reported several cases in which talc seems undoubtedly to be the etiologic agent. Antopol<sup>3</sup> has reported additional cases in which lycopodium was the agent responsible for a similar tissue reaction. Erb has reviewed the literature on lycopodium and added his experiences with some of these granulomatous lesions.

While the lesions histologically resemble those of tuberculosis, yet in none of them could *Mycobacterium tuberculosis* be found in preparations stained by Ziehl-Neelsen technique. A geologist whom we consulted believed that the crystals were undoubtedly talc, since crystals of other substances which resemble talc are not used in surgery. The crystals seen in the tissue examined by us belonged to the monoclinic system with extinction angles corresponding to those of magnesium silicate. We have reviewed sections in cases of known tuberculosis of the soft tissue and in none of these have crystals and amorphous material been seen.

The finding of talcum powder in pseudotubercles on the peritoneum in 1 case of regional ileitis and in another in which multiple abdominal operations had been performed was most interesting to us. The possibility of implanting talcum in cases of regional ileitis is enhanced because of the fact that multiple operations before resection are not uncommon, and also because the serosal surface of the intestine is injured by inflammation. In the reported Case 2 an operation for appendicitis had been done elsewhere, and after coming under our care, a preliminary ileocolostomy was done making two inoculations with powder probable. In none of the descriptions of ileitis have we found talcum mentioned as an agent which may be responsible for part of the pathologic picture. In spite of the fact that glove powder is responsible for these surgical complications, its advantages over the older wet glove technique are too great, in our opinion, to recommend a change to the latter. We would recommend that gloves be carefully washed in the hand basin after they are put on in order to eliminate as much powder as possible. Furthermore, a minimum of powder should be used both in the preparation of gloves and in the preparation of the hands. To be aware of this complication resulting from the use of glove powder and to avoid confusion in the diagnosis of nodules in abdominal incisions are the particular aspects of this subject which we wish to stress.

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CASE 3.—In the third case, a man upon whom suprapubic cystostomy had been performed, the microscopic picture was identical, and in Fig. 3*A* and *B* one can see again under ordinary light (Fig. 3*A*) and under polarized light (Fig. 3*B*) the microscopic findings in a section taken from a painful nodule in an old low midline incision.

CASE 4.—In the fourth case there were talcum powder granulomatous lesions both in the abdominal incision and upon the peritoneal surface of the intestine. The patient was a woman, 31 years of age, upon whom a panhysterectomy and bilateral salpingo-oophorectomy had been performed two months previously for papillary cystadenocarcinoma of the ovary. Three weeks after her original operation a secondary laparotomy had been performed for the relief of intestinal obstruction which developed during the postoperative period. The patient was admitted to the hospital some two months after her first operation because of a tender mass in the abdominal incision, the site of a previous enterostomy. Examination of this mass after removal showed it to be a foreign body granuloma, probably due to glove powder. At a later operation for intestinal obstruction the patient died from cyclopropane poisoning. At autopsy only one nest of cancer cells implanted upon the peritoneum of the ileum was seen. There was, however, an area of inflammatory reaction about the terminal ileum. Microscopic examination of the surface of the ileum in this region showed multiple tubercle-like structures in which foreign body giant cells containing a crystalline material similar to that seen in the lesions described.

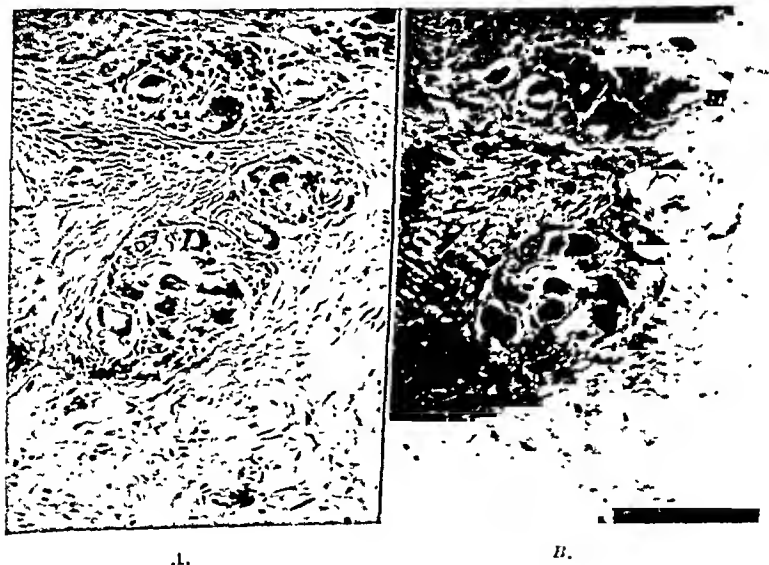


Fig. 3*A*.—Section from tissue removed in Case 3. The crystalline deposits and the foreign body giant cells were abundant. *B*, Photograph of same tissue as shown in *A* after polarization of light.

#### COMMENT

Surgical powder usually consists of magnesium silicate or talc, although lycopodium spores are sometimes used. The reaction of the body to the presence of lycopodium spores is quite similar, except for the fact that the spores, which are larger than crystals and are organized vegetable cells, are usually clearly visible in the lesions. Apparently, however, the lycopodium powder causes a higher percentage of reactions than does talc. Sinus tract formation is more liable to occur. Experi-

sections of the rhomboids and serratus muscles were dissected from the vertebral border of the scapula, and these muscles were separated from the latissimus dorsi and were not included with the extremities. The skin, omotransverse and brachiocephalic muscles were cut across just below the ascending cervical branch of the jugular vein and just above a group of lymph glands present in this region. The upper extremity was thus severed from the trunk.

The femoral vessels were exposed, cut, and ligated. The external genitals were removed from the pubis and the origins of the adductor muscles in the midline of the pubis were divided down to the symphysis. The muscles attached anteriorly to the external surface of the pelvis were freed from the bone, and the posterior extremity was thus severed from the trunk.

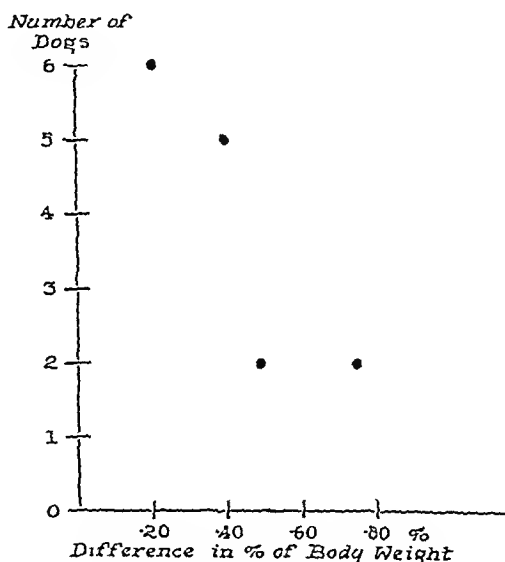


Fig. 1.

In this manner both extremities with superficial tissues of the trunk on each side were removed in one piece. Such dissection included fluid which had extravasated into the groins and flanks. The paired extremities of either side were weighed on a scale with an accuracy of 1 Gm., and these weights together with the total weight of the dog were recorded. The dissection and weighing were readily accomplished within an hour's time.

Fifteen control dissections and 6 dissections on traumatized dogs were performed. In 2 of the controls (Nos. 9 and 10) the method was further tested by injecting a known weight of blood into the extremities on one side. The amount of weight "recovered" was then compared to that injected.

## A TECHNIQUE FOR THE MEASUREMENT OF LOCAL FLUID LOSS IN EXPERIMENTAL TRAUMATIC SHOCK

M. L. CULLEN, M.D., AND N. E. FREEMAN, M.D., PHILADELPHIA, PA.

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University of Pennsylvania)*

IN THE course of experiments on traumatic shock, it became necessary to measure the amount of fluid lost into the traumatized extremities. The present experiments were undertaken to test the accuracy of measuring fluid loss by careful anatomical separation of the homolateral extremities with intervening tissue and comparing the weights of opposite sides.

### TECHNIQUE

After clipping the hair from the areas to be incised, with the dog placed on its abdomen, a midline incision was made from just below the base of the skull down over the middle of the spine to the tail. From the caudal end of this incision two oblique symmetrical incisions were made on either side of the tail and rectum. The superficial fascia and attachments of trapezius and latissimus dorsi muscles were divided close to the spinous processes. The origins of the latissimus dorsi were cleanly separated from the lumbodorsal fascia and the last two ribs. The erector spinal muscles were left on the trunk.

With the knife edge kept close to the pelvic bone, the mass of hip muscles was dissected from the external surface of the pelvis, and the muscles emerging from the pelvis were cut at their points of exit, except that the psoas muscles were cut at their insertions on the femurs. The capsules of hip joints were cut.

The dog was then placed on its back and a midline incision was made from the neck to the caudal end, from which point this incision was forked so as to pass around the external genitals to meet the dorsal oblique incisions. In the thoracic region the incision was extended down to the middle of the sternum and the pectoralis muscles were dissected from the chest wall. Care was taken to leave the attachments of the recti and external oblique muscles intact. In the region of the abdomen the skin and all the superficial fat and fascia were reflected from the abdominal muscles.

Skin and fascia were then dissected from the muscles of the neck laterally to the jugular vein. The subclavian vessels and brachial plexus were exposed. The vessels were ligated and divided. The in-

sections of the rhomboids and serratus muscles were dissected from the vertebral border of the scapula, and these muscles were separated from the latissimus dorsi and were not included with the extremities. The skin, omotransverse and brachiocephalic muscles were cut across just below the ascending cervical branch of the jugular vein and just above a group of lymph glands present in this region. The upper extremity was thus severed from the trunk.

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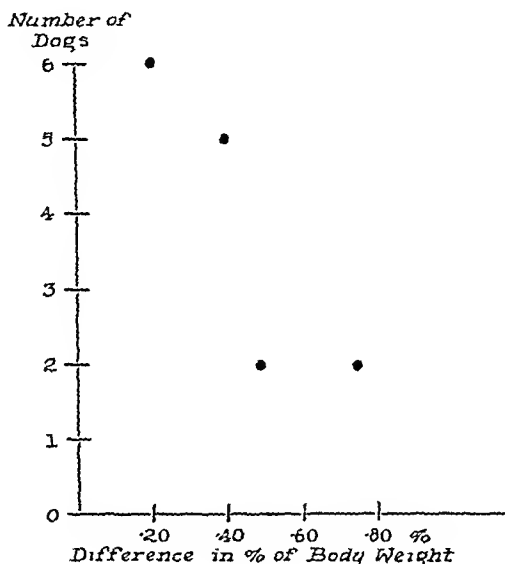


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## RESULTS

In 15 control dissections (Table I) an average difference with respect to body weight of 0.32 per cent was obtained. In 1 case (No. 10) a larger error resulted when the bisected part, which had been injected with blood, was allowed to rest in a pail, and there was leakage of some of the injected blood. In another case (No. 11) a larger error resulted possibly because the skin of one side was wet before the dissection. Excluding these errors, the control figures might have been lowered. Fig. 1 shows the distribution of difference in weight between the two sides expressed in terms of body weight. In 11 out of 15 control dissections, the difference was less than 0.4 per cent.

TABLE II  
LOCAL FLUID LOSS IN TRAUMATIZED DOGS\*

EX- PERI- MENT	WEIGHT (GM.)				FLUID LOSS AS PER CENT OF BODY WEIGHT	REMARKS
	TOTAL WEIGHT OF DOG	TRAU- MA- TIZED EX- TREM- ITIES	NOR- MAL EX- TREM- ITIES	DIF- FER- ENCE		
1	17,000	4,705	3,835	870	5.1	Recovered from trauma; sacri- ficed 7 hr. later; autopsy showed only signs of hemorrhage
2	13,900	3,400	2,800	600	4.3	Died 1 hr. after trauma in shock
3	7,200	1,780	1,410	370	5.1	Died 3 hr. after trauma in shock
4	12,700	2,825	2,340	485	3.7	Died 3½ hr. after trauma in shock
5	11,000	1,920	1,615	305	3.5	Died 4 hr. after trauma in shock
6	6,000	1,305	957	348	5.8	Died in shock 3½ hr. after trauma; previously partially sympathec- tomized, but left splanchnics were intact

\* Average difference, 496.3 Gm. average per cent loss in regard to body weight, 4.6.

In 6 dissections on traumatized dogs (Table II), an average difference of 4.6 per cent with respect to body weight was obtained. These figures approximate the figures on local fluid loss in comparable experiments by Blalock and others. In absolute figures there was an average "dissection" error of 32.3 Gm. in controls compared to an average difference of 496.3 Gm. in the dissections on traumatized dogs.

## DISCUSSION

Cannon and Bayliss<sup>1</sup> first attempted to measure local fluid loss in experimental traumatic shock by amputating the legs with symmetrical cuts across the upper thighs and comparing the weight of the traumatized leg with that of the opposite normal leg. It was later shown by Parsons and Phenister<sup>2</sup> and Blalock<sup>3</sup> that such measurements failed to include blood and fluid which extravasated into the groin and flank. Blalock modified their technique by making a midline abdominal incision, tying off the aorta and vena cava, clamping the iliac vessels,

In the traumatized experiments, trauma was performed by the technique of Kendrick, Essex, and Helmholz<sup>10</sup> The dogs were anesthetized with ether and 1,500 blows with a rubber hammer were administered over a forty-minute period to both the fore- and hindmuscles on one side.

TABLE I  
CONTROL DISSECTION EXPERIMENTS

EX- PERI- MENT	WEIGHT (GM)				FLUID LOSS AS PER CENT OF BODY WEIGHT	REMARKS
	TOTAL WEIGHT OF DOG	LEFT EX- TREM- ITIES	RIGHT EX- TREM- ITIES	DIFFER- ENCE		
1	15,000	2,715	2,730	15	0.10	Normal male accidentally killed under ether
2	9,700	1,770	1,820	50	0.51	Postoperative death (bilateral abdominal sympathectomy); previous thoracic sympathectomy
3	5,400	970	975	5	0.09	Postoperative death (bilateral stellate ganglionectomy and abdominal sympathectomy)
4	5,000	860	866	6	0.12	Same circumstances as in No 3
5	6,000	1,168	1,139	29	0.48	Same circumstances as in No 3
6	5,300	562	574	14	0.26	Same circumstances as in No 3
7	10,500	2,330	2,296	34	0.32	Died 2 days after severe bleeding, moderate hematoma in right thigh, obese
8	13,500	1,645	1,700	55	0.40	Killed by chloroform, lying on right side several hours before dissection
9	5,700	883*	880	3	0.05	Tested for recovery of blood in injected into thigh muscle
10	5,400	850†	810	40	0.74	Died from peritonitis, tested as in No 9, but there was leakage of injected blood before the weighing was done
11	13,600	2,815	2,710	105	0.77	Lying on left side many hours before dissection, fur on this side wet
12	17,400	3,155	3,200	45	0.20	Normal male accidentally killed under ether
13	5,000	523	538	15	0.30	Died 10 days postoperatively of distemper and pneumonia
14	5,300	625	636	11	0.20	Died 3 wk postoperatively; pneumonia and pleural effusion
15	14,900	1,999	1,942	57	0.38	Died 24 hr. postoperatively, massive consolidation of right lung
Average				52.2	0.32	

\*Total weight of this extremity at dissection was 1,133 Gm minus 250 Gm injected for testing recovery equals 883 Gm

†Total weight of this extremity at dissection was 1,110 Gm minus 310 Gm injected for testing recovery equals 850 Gm



## RESULTS

In 15 control dissections (Table I) an average difference with respect to body weight of 0.32 per cent was obtained. In 1 case (No. 10) a larger error resulted when the bisected part, which had been injected with blood, was allowed to rest in a pail, and there was leakage of some of the injected blood. In another case (No. 11) a larger error resulted possibly because the skin of one side was wet before the dissection. Excluding these errors, the control figures might have been lowered. Fig. 1 shows the distribution of difference in weight between the two sides expressed in terms of body weight. In 11 out of 15 control dissections, the difference was less than 0.4 per cent.

TABLE II  
LOCAL FLUID LOSS IN TRAUMATIZED DOGS\*

EX- PERI- MENT	WEIGHT (GM.)				FLUID LOSS AS PER CENT OF BODY WEIGHT	REMARKS
	TOTAL WEIGHT OF DOG	TRAU- MA- TIZED EX- TREM- ITIES	NOR- MAL EX- TREM- ITIES	DIFFER- ENCE		
1	17,000	4,705	3,835	870	5.1	Recovered from trauma; sacrificed 7 hr. later; autopsy showed only signs of hemorrhage
2	13,900	3,400	2,800	600	4.3	Died 1 hr. after trauma in shock
3	7,200	1,780	1,410	370	5.1	Died 3 hr. after trauma in shock
4	12,700	2,825	2,340	485	3.7	Died 3½ hr. after trauma in shock
5	11,000	1,920	1,615	305	3.5	Died 4 hr. after trauma in shock
6	6,000	1,305	957	348	5.8	Died in shock 3½ hr. after trauma; previously partially sympathectomized, but left splanchnics were intact

\*Average difference, 496.3 Gm.; average per cent loss in regard to body weight, 4.6.

In 6 dissections on traumatized dogs (Table II), an average difference of 4.6 per cent with respect to body weight was obtained. These figures approximate the figures on local fluid loss in comparable experiments by Blalock and others. In absolute figures there was an average "dissection" error of 32.3 Gm. in controls compared to an average difference of 496.3 Gm. in the dissections on traumatized dogs.

## DISCUSSION

Cannon and Bayliss<sup>1</sup> first attempted to measure local fluid loss in experimental traumatic shock by amputating the legs with symmetrical cuts across the upper thighs and comparing the weight of the traumatized leg with that of the opposite normal leg. It was later shown by Parsons and Phemister<sup>2</sup> and Blalock<sup>3</sup> that such measurements failed to include blood and fluid which extravasated into the groin and flank. Blalock modified their technique by making a midline abdominal incision, tying off the aorta and vena cava, clamping the iliac vessels,

splitting the symphysis pubis with a saw, removing the rectum and bladder, and bisecting the carcass in the midabdominal region. He then divided the hind end of the animal by sawing down the middle of the vertebral column. In a later article Blalock<sup>4</sup> described another method for measuring local fluid loss in experimental burns. This technique consisted in removing all abdominal and thoracic contents, sawing off the head in the plane of symmetrical transverse cervical incisions, sawing through the symphysis pubis, and removing the vertebral column and tail en masse by sawing across all the costovertebral junctions and the sacroiliac joints. The animal was thus bisected. No control figures were given to show the accuracy of this method. More recently Harkins,<sup>5</sup> using Blalock's second technique, gives the results on bisections of 7 normal animals. He found an average difference between the two sides equivalent to 0.38 per cent of body weight. Harkins has also devised a method (Nos. 6 and 7) for measuring fluid shifts continuously in experimental burns by the use of a "tipping" apparatus. While this technique is useful in studying the time of weight increase in the case of burns, it does not appear to be practicable in trauma experiments. Best and Solandt<sup>6</sup> are at present measuring local fluid loss after trauma by means of displacement of water. They then dissect out any tissue in the groin and flank containing blood which has collected there and add it to the weight of the limb. A detailed description of this work has not yet appeared in the literature.

The method described in this paper of measuring local fluid loss by anatomical dissection is not without error, but the error is small in comparison to the difference in weight observed in "trauma" experiments. The error is theoretically less than that occurring in the use of Blalock's bisection technique, since less tissue unaffected by trauma is included. In addition, the use of simple dissection appears to have the advantage of speed over the necessity for using a saw, as in Blalock's method.

With practice in the dissection the error can be made still lower. The results in the last 4 dissections (the figures are listed chronologically) indicate a smaller error, 0.27 per cent, than in those of the earlier dissections.

The use of comparative weights of normal and traumatized limbs as a measure of local fluid loss has been criticized<sup>9</sup> on the grounds that a large portion of the fluid in the traumatized area comes from the normal side, thus doubling the error. This argument appears to be fallacious in view of the fact that the extravasated fluid in the area of trauma comes from the rest of the body as well as from the normal extremities.

#### SUMMARY

A method is described for the measurement of local fluid loss in experimental traumatic shock.

In 15 control experiments an average error equivalent to 0.32 per cent of body weight was obtained.

In 6 trauma experiments there was an average local fluid loss equivalent to 4.6 per cent of body weight.

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## CAJEDROL

### A NEW ANALGESIC AND ANTISEPTIC FOR THE GENITOURINARY SYSTEM

CHARLES F. ELVERS AND CARL E. BURKLAND, BALTIMORE, MD.

(From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital)

SEVERAL years ago one of us (C. F. E.) noted that among the many patients treated at the Brady Urological Institute for interstitial cystitis, tuberculosis of the bladder, tumors of the bladder, etc., a small percentage obtained considerable relief from their acute symptoms, as well as from the discomfort following fulguration and instrumentation, if a small quantity of oil of niaouli was injected into the bladder immediately after the treatment was given.

Although this was effective in many cases, the results were not all that could be desired and a number of patients were found who did not react favorably to the niaouli.

In the preparation used, the active principle consisting of oil of niaouli is carried in a medium of olive oil, the viscosity of which makes its injection into the bladder difficult unless a special pelvic syringe of fairly large caliber is used. It was available in the United States as a proprietary product only, the supply then being limited, and at present being rather difficult to obtain.

Because of the results obtained in favorable cases following the distillation of this solution, it seemed highly desirable that a preparation be produced which would contain all of the elements of medicinal value found in niaouli oil, and in addition, be more highly bacteriostatic, non-irritating, and of a viscosity which would permit its being easily injected through catheters or instruments of small caliber.

A survey of the list of products derived from numerous plants of the Myrtaceae family and particularly the species *Melaleuca*, the group from which niaouli oil is obtained, revealed an interesting group of oils containing alcohols, aldehydes, terpenes, etc., of considerable medicinal value, most of which have been in general use in the Orient for centuries and some of which are now recognized and described in the materia medica of Europe and America.

Among this group of oils one was found which seemed to possess practically all of the desirable features for which we were seeking. This was cajeput oil, the essential oil extracted by distillation from the fresh leaves and twigs of *Melaleuca leucadendron*, usually the variety known as *Cajeputi viridiflora*, a shrub common to all of the East Indies Islands. The most valuable constituent of this oil appears to be the alcohol cajeputol ( $C_{10}H_{18}$ ), a variety of cineol.

It is said to act as a carminative, stimulant, diaphoretic, parasiticide, and antiseptic. It is nonirritating and effective when dissolved in

neutral fixed oils in dilution of 5 per cent. The redistilled oil which is official in the *Pharmacopoeia of the United States of America* should be specified for medicinal uses.

For a long time benzoin has been accepted as one of the best preservatives for fatty ointment bases, especially for lard, and it is generally conceded that its preservative strength increases with its hydroxybenzoic ester content. Parahydroxybenzoic acid esters have proved also to be of considerable value as preservatives for solutions containing alkaloids used in the treatment of eye conditions, more particularly in cases of surgery of the eye.

In their research work with animals Schubel and Manger demonstrated that the toxic effect of the disinfectant here used in effective dilution is so slight that it may be disregarded.

Sabalitschka in his studies of the germicidal value of the various esters of parahydroxybenzoic acid found that the propyl ester remained effective in a dilution of 0.05 per cent as here shown in his tables (Tables I and II).

TABLE I<sup>1</sup>

MIXED CULTURES OF STAPHYLOCOCCI, STREPTOCOCCI, AND B. COLI OBTAINED FROM HEAVY ORBITAPHLEGMON

PROPYL P-HYDROXY-BENZOATE	CONCENTRATION			
	0.03%	0.04%	0.05%	CONTROL
24-hr. culture	++	+	-	++++
48-hr. culture	++	+	-	++++
72-hour culture	++	+	-	++++

TABLE II\*

PNEUMOCOCCUS WITH LEVITHAL AGAR

PROPYL P-HYDROXY-BENZOATE	CONCENTRATION	
	0.05%	CONTROL
24-hr. culture	-	++
48-hr. culture	-	++

\*The tabulation is taken from the report of Sabalitschka.<sup>2</sup>

Staphylococcus and mixed cultures in bouillon with 0.1 per cent parahydroxybenzoate were negative by re inoculation after twenty-four hours. Sabalitschka further states that the growth obtained from the above organisms on Levithal agar corresponded to results with other bacteria on agar-agar and the investigations with liquid nutrient media were in general somewhat better than on solid nutrients.

Since this propyl ester of parahydroxybenzoic acid is nonirritating, bacteriostatic in high dilutions, and directly soluble in oil, it has been used in the preparation of cajedrol in a dilution of 0.1 per cent.

As a medium to carry the cajepnt oil and hydroxybenzoic ester we found the most desirable to be *Olcum archis* (American peanut oil, edible variety). This bland fatty oil has low viscosity, is nonirritating and an excellent solvent for volatile oil. It is light, less viscous, and less prone to rancidity than the olive oil or sweet almond oil generally

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CASE 3.—H. D. (BUI 30245), a 64-year-old woman, had an ulcer of the bladder which had resulted from treatment elsewhere of carcinoma of the cervix with radium. She suffered from frequency, burning, pain, and strangury. Moderate relief followed the instillation of cagedrol every day for a week.

CASE 4.—F. E. T. (BUI 30403), a 59-year-old white man, had a history of chronic prostatitis, vesiculitis, and prostatic calculi. Culture of the urine yielded *Staphylococcus aureus*. He was improved by prostatic massage and diathermy, and the urine was rendered sterile by the use of sulfathiazole, but he still had moderate frequency, urgency, and some nocturia which were greatly alleviated by triweekly instillations of cagedrol into the bladder over a period of two weeks, after which he returned to work. Within two months his bladder capacity increased from 40 to 250 c.c.

CASE 5.—H. G. (BUI 27268), a 43-year-old woman, had chronic urethritis. She complained considerably of frequency, burning on urination, and urgency which did not respond to the usual forms of treatment, but upon having instillations of cagedrol on three occasions the symptoms were very markedly relieved.

CASE 6.—S. S., a woman 50 years of age, had chronic urethritis and urinary tract infection which was improved by the administration of sulfanilamide and local treatment for the urethritis, but moderate burning, urgency, and some frequency persisted. These symptoms were considerably alleviated by a few instillations of cagedrol.

CASE 7.—Z. M. (BUI 25570), a woman 41 years of age, had right renal tuberculosis and tuberculous cystitis. She suffered from marked burning, frequency, and nocturia. Following several injections of cagedrol she noted a decrease in the burning and absence of nocturia. Cystoscopy disclosed considerable improvement in the ulceration along the base of the bladder.

CASE 8.—W. S. (BUI 22442), a white man 50 years of age, returned after an absence of eight years because of terminal hematuria, marked frequency, burning, and urgency. Cystoscopy revealed a contracted bladder and marked cystitis. The urine was cloudy. He was given hydraulic dilatation of the bladder and instillations of cagedrol, 1 ounce, three times a week, for two weeks. Two months later there was marked alleviation of symptoms. He had only slight frequency, no urgency or burning, and the urine was clear. His bladder capacity had increased from 60 to 360 c.c.

CASE 9.—J. S. (BUI 28869), a woman 43 years of age, with urinary tract infection and chronic urethritis, suffered considerably from bladder spasms, nocturia, burning, and urgency. She was treated by antiseptics by mouth and local applications of nitrate of silver to the urethra, but only after being given cagedrol did she obtain considerable relief from her severe symptoms.

CASE 10.—N. A. (BUI 25688), a 71-year-old white man, following prostatectomy some years previously, returned with cloudy urine, considerable urgency, frequency, and burning. His bladder capacity was 50 c.c. He improved considerably following forced fluids and irrigations of the bladder with sulfathiazole, but the burning and urgency disappeared only after the instillation of cagedrol daily for ten days. The bladder capacity increased to 400 c.c.

CASE 11.—L. D. (BUI 1924), a middle-aged white man with a tumor of the bladder of long duration was given cagedrol two to three times a week for two months. The bladder capacity increased considerably; the frequency and urgency decreased.

We are indebted to Dr. Humphrey D. Wolfe, of Wilmington, Del., for a report on a series of cases in which he has employed intravesical injections of cagedrol.

used in similar preparations. The oils and esters here described and used in making cajedrol are U.S.P. standard and are used in the following proportions:

Parahydroxybenzoate (propyl)	1 Gm.
<i>Oleum cajeputi</i>	50 c.c.
<i>Oleum archis</i> in quantity sufficient to make 1 liter	

These are readily obtainable in the United States and at comparatively low cost.

The effectiveness of cajedrol as an agent in relieving the distressing symptoms in many types of acute and chronic cystitis and other pathologic conditions of the bladder appears to be directly due to the therapeutic effect of the essential oil of *cajeputi* plus the additional antiseptic or bacteriostatic action of the oil-soluble propyl ester of parahydroxybenzoic acid. The bland medium *Oleum archis* serves as a coating and protective film on the surface of the bladder wall.

During the past three years at the Brady Urological Institute we have used cajedrol in place of gomenol, which we formerly got from France. We have found cajedrol a soothing analgesic and a mild antiseptic. Cajedrol alleviates the distressing symptoms of various types of cystitis and other painful lesions, bladder tumor, prostatitis and vesiculitis, and the irritation that often follows instrumentation of the urethra and bladder. It is helpful in relieving bladder spasms which often are associated with these conditions, as well as allaying the symptoms of marked frequency, urgency, burning, strangury, and pain. We usually instill 10 to 15 c.c. into the bladder through a catheter at daily or bi-weekly intervals. Cajedrol is not a cure-all, but used in conjunction with established therapeutic procedures, it sometimes affords relief from distressing symptoms. In a few cases cajedrol has been injected up the ureter during the use of the Couceill stone extractor and has facilitated withdrawal of this instrument when there has been some difficulty due to spasm of the ureter. We have noted no reactions or aggravation of symptoms in any patient from its use.

The following are examples of cases in which particular relief has been noted from the instillation of cajedrol into the bladder and urethra.

CASE 1.—M. G. (BUI 30325), a 38-year-old Greek housewife, had tuberculosis of the left kidney, ureter and bladder. Following left nephroureterectomy she complained of marked frequency, burning, urgency, and suprapubic discomfort and bladder spasms from ulcerative cystitis. The urine was cloudy and the bladder inflamed and ulcerated. An instillation of 1 ounce of cajedrol was made into the bladder daily for three weeks. Her symptoms were greatly alleviated, the urine became clear, and on cystoscopy the inflammation and ulceration of the bladder had decreased greatly.

CASE 2.—Mrs. F. G. A. (BUI 26856), a white woman, 38 years of age, had chronic urethritis and polyps of the bladder. She complained of great frequency, pain, and urgency of urination. She obtained relief from dilatation of the urethra, application of nitrate of silver to the urethra, fulguration of the polyps, and instillation of cajedrol, 1 ounce, on three occasions.



CASE 3.—H. D. (BUI 30245), a 64-year-old woman, had an ulcer of the bladder which had resulted from treatment elsewhere of carcinoma of the cervix with radium. She suffered from frequency, burning, pain, and strangury. Moderate relief followed the instillation of cajedrol every day for a week.

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CASE 12.—L. E. H., a 41-year-old man, complained of hematuria, marked frequency, and tenesmus. On cystoscopy the bladder was inflamed and congested, and there were numerous areas of submucosal hemorrhage. One bleeding area was fulgurated. Biopsy showed only necrotic material. He was given a daily instillation of 8 c.c. of cajedrol for seven days with relief of the urgency and frequency. Cystoscopy one month later showed marked improvement in the condition of the bladder and only a few discrete inflammatory lesions present. The bladder capacity increased from 45 to 260 c.c. within five weeks.

CASE 13.—L. G., a 44-year-old white man, complained of gross hematuria and frequency. On cystoscopy the bladder capacity was found to be markedly reduced. There were numerous hemorrhagic areas throughout the bladder, the mucosa of which had the appearance of raw beef. He was given daily instillations of cajedrol, 8 c.c., for ten days. His symptoms promptly disappeared. Examination of the bladder six weeks later showed a normal capacity and a normal mucosa, except for a few areas of congestion on the left lateral wall.

CASE 14.—L. R., a white man 53 years of age, had had periodic fulgurations of a bladder tumor for several months, but he usually was disturbed with painful bladder spasms and burning following these treatments. Intravesical injections of cajedrol, 10 c.c., resulted in marked benefit.

CASE 15.—H. M., a 65-year-old white man, who had been treated by fulguration and radium for a bladder tumor, had been bothered with marked frequency, nocturia, urgency, and burning. Daily injections of cajedrol, 10 c.c., resulted in marked relief of the frequency, nocturia, and stranguary.

#### SUMMARY

Products derived from plants of the Myrtaceae family have long been known to have considerable medicinal value. Of these cajeput oil has been shown to be of marked value. After much experimentation in the laboratory and clinic a combination of parahydroxybenzoate (propyl), *Oleum cajeputi* and *Oleum archis* was found to be a valuable compound for the relief of the distressing symptoms and many types of acute and chronic cystitis and other pathologic conditions in the bladder. This compound, to which the name cajedrol has been given, now has been used in many clinical cases. Brief abstracts of some of these cases have been presented. Cajedrol has proved to be a soothing analgesic and a mild antiseptic and a useful adjunct along with other well-established therapeutic procedures for the relief of distressing symptoms of general cystitis, interstitial cystitis, prostatitis, and also urethritis in the male and female. In some cases of marked ulceration of the bladder and tumor of the bladder, great improvement has been noted, as well as after instrumentation of the urethra and bladder. A marked increase in the capacity of the bladder has been noted in cases that received instillations of cajedrol. Other details showing the value of cajedrol in various vesical and urethral lesions have been cited.

Grateful acknowledgment is hereby made to Robert S. Fuqua, Chief Pharmacist, Johns Hopkins Hospital, for his valuable assistance and suggestions in the preparation of this paper. We wish also to express our appreciation to Dr. E. K. Marshall for his interest and advice on reviewing the manuscript.

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# MALIGNANT DEGENERATION IN A CASE OF MULTIPLE BENIGN EXOSTOSES

WITH A BRIEF REVIEW OF THE LITERATURE

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A CLEAR conception of the type of tumor with which we are dealing seems the best approach to this subject. The literature abounds with long and detailed classifications of cartilaginous and osteocartilaginous tumors, such as enchondroma, eechondroma, osteochondroma, chondrodysplasia, etc. All these terms serve merely to differentiate bone tumors of cartilaginous nature according to the amount of calcified tissue they contain, their location, and their number. But they are all closely related, the enchondroma or chondroma being the most distant relative of the group in that it is almost completely cartilaginous in nature, occurs in the shaft of the bone, and frequently becomes malignant. On the other hand, all of the other mentioned types of tumors rarely undergo malignant change and occur most frequently in the metaphyseal region of the bone where it is believed an abnormality of development takes place. This consists in either a complete or partial arrest of periosteal extension across the metaphysis. Thus, there is lacking the usual limiting membrane of periosteum across the area and the underlying cartilage no longer has a restricted area of growth. Consequently an overgrowth of cartilage develops and tumor formation occurs. As these tumors become more mature, however, the cartilage usually becomes normal bone. Therefore, we feel justified in referring to them simply as exostoses. Certainly, their appearance in the x-rays below simulates that of bone of normal density. (Fig. 1.)

Actually, many years ago benign exostoses and chondromas were thought to be entirely different in composition, but as early as 1905 Lenormant<sup>1</sup> reported a number of analogies between the two conditions. Research progressed along these lines until in 1939 Kress<sup>2</sup> wrote that these two tumors are of the same origin but that exostoses are chronologically older and are fairly in line with normal bone development and that chondromas are composed of much younger tissue and, as is generally true of such tissue, undergo malignant change much more frequently.

## CASE REPORT

The history of this case of multiple exostoses is as follows: On May 15, 1940, while playing at school, the patient, a 10-year-old boy, was knocked down and the lateral side of the right thigh was bruised. The injury was not a severe one and was not disabling but served to attract the patient's attention to this region of

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his leg where a swelling was now noted for the first time. It was tender and x-rays made at the time revealed the presence of a bone tumor. There was no history of weight loss or of other swellings or areas of tenderness.

The family history is best illustrated by the diagram shown in Fig. 2. From this it is seen that the disease affects both males and females alike and follows no laws of inheritance. Also, it is important to note that the patient is the only member of his family afflicted with malignant degeneration. The latest addition



-1.

Fig. 1.—X-rays of the patient's left shoulder and knee, showing multiple benign exostoses.

to the family (represented by the solid circle in the extreme lower right portion of the diagram) was only 5 months of age at the time his x rays were made, but close observation reveals several prominences in the metaphyseal regions that are very suggestive of the tumors found in his older relatives (Fig. 3). Thus, we believe, is one of the youngest known cases of multiple exostoses, the only other that approaches it being that of a 6-month-old child reported by Scott.<sup>3</sup>

Examination of this well-nourished, 10-year old boy revealed a swelling of the right leg, just above the knee, on the lateral surface of the thigh, about two by two



Fig. 1B.—See opposite page for legend.

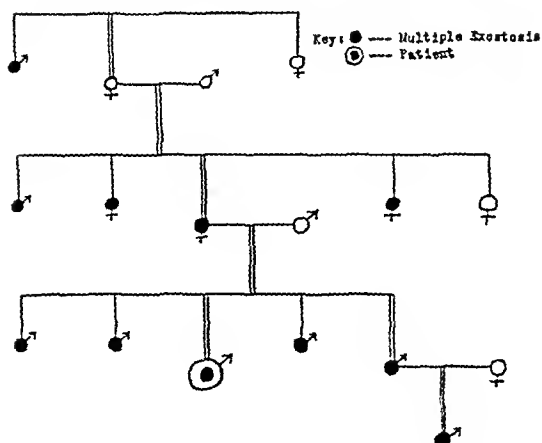


Diagram of the Family History

Fig. 2.—Diagram of the family history. From this it is seen that the disease affects both males and females alike and follows no laws of inheritance. Also, it is important to note that the patient is the only member of his family afflicted with malignant degeneration.

and one-half inches in size. It was hard and tender and a few superficial veins were seen in the overlying skin. X-rays revealed multiple exostoses scattered throughout the skeletal system. The one noted at the lower end of the right femur, however, was much more sclerotic than any of the others and, in addition, there was considerable periosteal reaction and some destruction of the cortex (Fig. 4). Accordingly, the tumor was biopsied and the section diagnosed as osteogenic sarcoma. Dr. A. Rieh, of the Johns Hopkins Medical School, pointed out the intense



FIG. 3.—X-rays of the patient's five-month-old nephew, showing the lower ends of the right forearm and left upper leg.

cellular growth activity with frequent mitotic figures in the section shown in Fig. 5. A great variety of cells is present. There are large cells with large, hyperchromatic nuclei; smaller cells with pale, indefinite cytoplasm and containing oval or irregular-shaped nuclei; spindle-shaped cells and several other types of less frequent occurrence. Among these are scattered osteoid spicules forming a sort of "lattice work." (Fig. 5.) X-rays of the chest, however, were negative and there was no glandular enlargement indicative of metastases. The child's parents,

however, refused permission for additional operative procedures and preferred resorting to deep x-ray therapy, although authorities agree that this is effective to only a slight degree in this type of tumor. This treatment was administered three times a week during the month of August, 1940, but since then it has been given only twice a week. By using alternating sides of the leg for approach, x ray burns have been avoided and treatment has been uninterrupted. Follow-up x-rays have revealed that the tumor is slightly increased in size and that it is becoming increasingly sclerotic (Fig. 6). The chest continues clear. The patient looks well and there are no evidences of metastases.

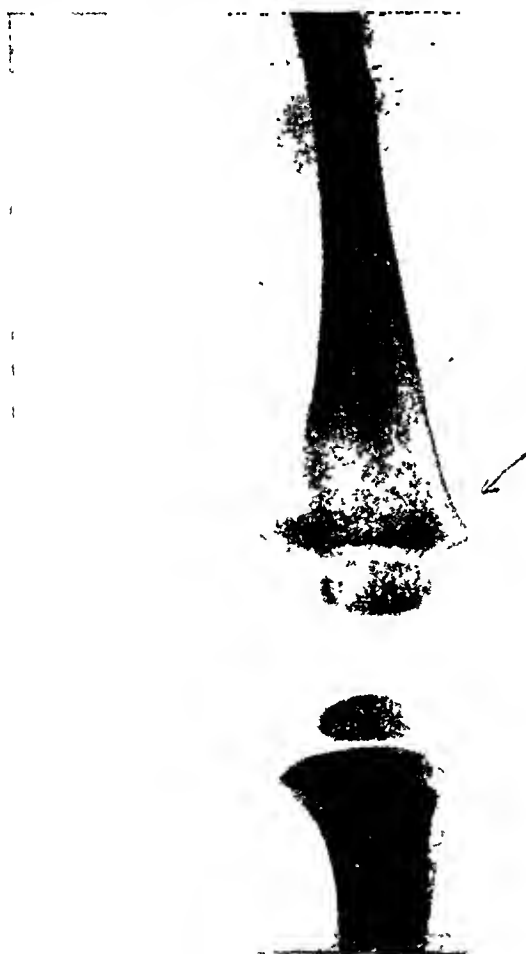


Fig. 3B—See opposite page for legend

It is impossible to make any conclusive statements regarding these malignancies on the basis of the limited number of cases at our disposal, but certain generalizations do seem to be taking form. First of all, the frequency of malignant degeneration in cases of multiple, benign exostoses seems to have been greatly exaggerated and apparently many conflicting statements have been made regarding this point. Most references and series, however, relate to single exostoses in which cases

Geschiekter and Copeland<sup>12</sup> state that malignant degeneration occurs so frequently as to be present in 7 per cent of all cases. This figure seems abnormally high and may well be explained by the fact that the vast majority of ordinary exostoses are asymptomatic and are never seen by physicians. Usually a doctor is consulted only when they become painful or produce paralysis through impingement on a nerve or suddenly



Fig. 4—X-rays of the lower end of the right femur

increase in size, as is the case in malignant degeneration. No substantial series of malignant degeneration in cases of multiple exostoses has ever been compiled; in fact, isolated case reports occurring at very infrequent intervals are all that the literature has to offer. American authors present three clear-cut cases. One is that reported by Jeek<sup>2</sup> in a patient in whom one of a number of enchondromata underwent



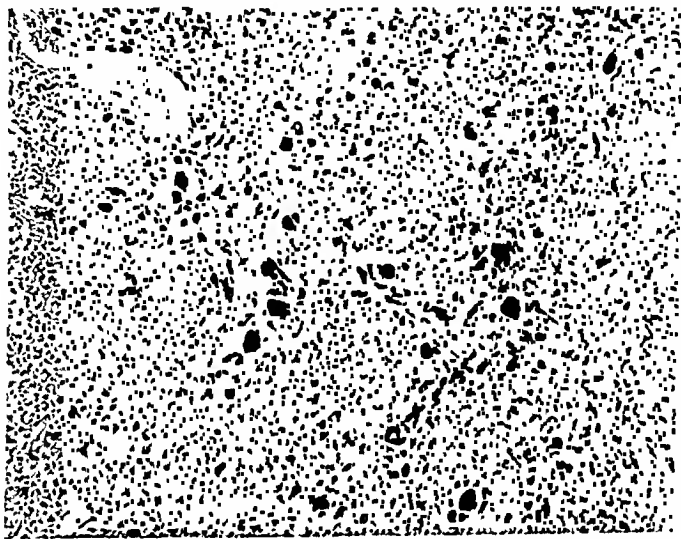
malignant change and then invaded the bladder. Fennel,<sup>6</sup> in 1938, described another occurring at the site of an exostosis of the femur and Codman had a patient whose leg, and later, whose arm, he had to amputate because of malignant degeneration of an exostosis of the femur and of the humerus. Ehrenfried,<sup>7</sup> in 1915 reviewed multiple exostoses in general and was able to report only twelve cases; of these he does not give any case history or evidence of their malignancy, yet states that



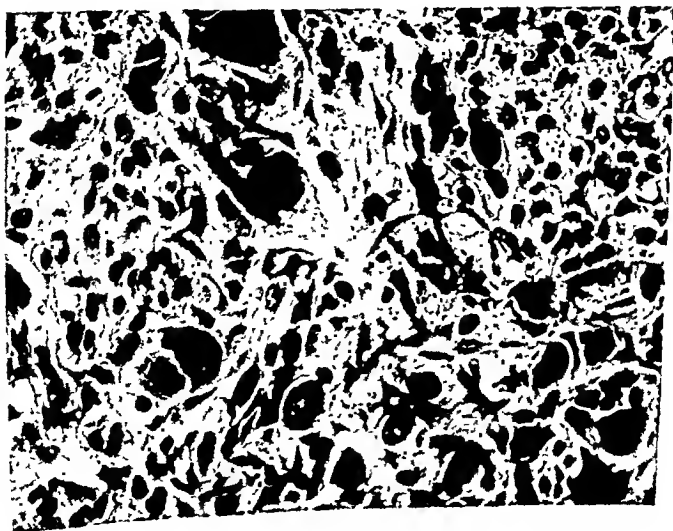
Fig. 1B.—See opposite page for legend.

malignant degeneration occurred in 5 per cent of all cases. He quotes two French authors, Lenormant and Lecene, who in 1905 collected twenty-four cases, most of which were fatal; but, in view of the infrequency of this change, it is hardly probable that such degeneration was the cause of these fatalities. Also, isolated and infrequent cases have been reported in the foreign literature: Belot and Simchowitz,<sup>8</sup> in 1936,

reported a well-established case of malignancy evolving from one of many benign exostoses, this occurring in the humerus; and Ciechanowski,<sup>9</sup> writing in the same year, reported a case of spindle-cell sarcoma in a patient with multiple exostoses. This terminated fatally, there being metastases in the liver. Didier,<sup>10</sup> in 1935, reported a case of chondrosarcoma of the sternum following the resection of a benign exostosis from the same site. And finally, Gardner,<sup>11</sup> in 1937, reported two cases that underwent malignant change. Both were treated with deep x-ray therapy; the one died of heart failure and the other was living at the



A.



B.

Fig. 5.—Microscopic views of the section biopsied from the lower end of the right femur. A, Low power ( $\times 100$ ); B, high power ( $\times 400$ ).

time the paper was published in 1939. In short, a review of the literature reveals that malignancy does occur in cases of multiple benign exostoses, but that it is a rare and infrequently reported complication. It is interesting to note that the later writers all consider malignant degeneration a very rare development in these cases, in contradistinction to the earlier authors who really had fewer and less convincing case reports but who spoke rather rashly of the relatively great frequency with which such tumors underwent malignant change.

The pathologic picture presented by those exostoses which undergo malignant degeneration is generally reported as that of an osteogenic sarcoma, although cases of chondrosarcoma and spindle-cell sarcoma have been described. Geschickter<sup>13</sup> feels, however, that these osteogenic sarcomas usually contain more cartilaginous tissue than does this case in which the "lattice work" seemed composed entirely of osteoid spicules. But in marked contrast to the usual short duration of life with early metastases, which is the usual story accompanying these tumors, most cases of malignant change occurring in a pre-existing exostosis have relatively long life spans. This may be explained by Copeland's<sup>14</sup> statement that osteogenic sarcoma is a term loosely applied to a group of bone tumors that differ markedly in their histology and degree of malignancy. At any rate, Fennel, whose case we have previously mentioned, reported an Hawaiian named Hong Mun, but who was better known as "Knobby Willy—the Exostotic Kid," in whom malignant degeneration occurred at the site of an exostosis of the femur. A sharp and thorough dissection was carried out, the patient refusing amputation. Pathologic sections confirmed the diagnosis of osteogenic sarcoma. Follow-up treatment consisted only of the implantation, for twenty-four hours, of some radium seeds. Thirteen and one-half years later the patient was perfectly well and actively employed at house painting. Codman's case, too, was free from recurrence ten years after the amputation of a leg and an arm. Gardner's cases, which were treated with deep x-ray for several years, died of causes other than metastases. So it does seem highly probable that Codman's suggestion in 1925 that osteogenic sarcoma arising in an exostosis has a better prognosis than the usual kind was a clear prediction of future findings.

There has been some speculation, too, regarding the factor concerned in the malignant degeneration of these exostoses. In this case there was a history of trauma, but this injury served only to lead to discovery of the tumor and x-rays taken several weeks later showed malignant change of a degree incompatible with the length of time intervening between the date of injury and the x-ray. Kress feels that an exogenous factor, such as trauma, is concerned but that also an hereditary factor is present. In contradiction of both of these theories is the case history of our patient as well as those of two even more completely investigated cases reported by Gardner. In all three instances the patients were

the only members of their respective families so afflicted; but of the seven or eight complete histories found in the literature, the traumatic factor is present in approximately 70 per cent. At the present time it seems that the fundamental elements concerned in the malignant degeneration of a benign exostosis remain rather obscure, yet trauma does seem of some importance.



Fig 6 —X-rays of the lower end of the right femur in July, 1910 (A), and November, 1910 (B).

Finally, there is the question of treatment. We believe that most surgeons would feel as did Rich, who upon looking at a microscopic section of this tumor said: "If that tumor were in my leg, I should want it amputated immediately." Certainly, the extremely malignant appearance of these sections would provoke such a reaction, yet because of the

natural objections to amputation as well as the inability to guarantee against metastases or recurrence, there are a number of cases similar to this in which amputation was refused and deep x-ray was used. Geschickter, however, states that osteogenic sarcomas respond in only "slight degree" to such therapy. Similarly, the observers of the New York Memorial Hospital feel that deep x-ray has no effect at all on these malignancies. Yet our patient at the present time has no evidence



Fig 6B—See opposite page for legend

of metastases and his tumor has increased only slightly in size. Gardner reports a case in which deep x-ray was used for two and one-half years, at which time the patient died of heart failure. He does state, however, that the tumor mass became larger during the course of treatment and that the patient became very emaciated. There are positive records of

long-term cures following amputation, Codman reporting one of ten years, Boyer another of eighteen years, and Fennel one of thirteen and one-half years. In view of these facts, it would seem that amputation is the treatment of choice, but in those cases which are inoperable or in patients who refuse amputation a trial with deep x-ray therapy certainly seems indicated.

#### SUMMARY

1. A case of multiple, familial, benign exostoses in which malignant degeneration evolved from one of the exostoses is described.

2. Malignant degeneration of multiple exostoses is a rare complication.

3. The fundamental cause of malignant degeneration in multiple exostoses is obscure, although trauma seems a factor.

4. The type of malignancy most frequently complicating cases of multiple exostoses is an osteogenic sarcoma.

5. The osteogenic sarcoma complicating multiple exostoses is a less malignant form than that usually encountered.

6. The treatment of choice is amputation, but the use of deep x-ray therapy is indicated in those patients refusing such an heroic measure and in those cases which are inoperable.

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## THE PARATHYROID GLANDS MALIGNANT TUMOR WITH OSTEITIS FIBROSA CYSTICA

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THE parathyroid glands, usually four in number, grow as paired structures from thickenings of the endoderm of the third and fourth branchial pouches. Their development is entirely independent of the thyroid gland. The superior pair of glands arise from the fourth pouches and are sometimes called "glandulae parathyroideae IV." The inferior pair are derived from the third pouches and are sometimes called "glandulae parathyroideae III." This transposition is brought about by the caudal migration of the branchial derivatives during which the thyroid gland and the "glandulae parathyroideae IV" have been outdistanced.

The extremely close relationship of the parathyroid glands to the thyroid and thymus is accountable for the not infrequent presence of one or more parathyroid bodies within the tissues of these two glands. Although thymus tissue has been found within the parathyroid glands, no thyroid tissue has ever been discovered therein.

A human being usually possesses four parathyroid glands. However, many variations in number have been found. In some cases experienced dissectors, such as Valkauyi,<sup>1</sup> have been able to find only one gland. MacCallum<sup>2</sup> has been able to find five pairs of these glands in one person. Symmetry may not be constant. Failure to find at least four glands may be attributed to one or more of the following causes: (1) congenital absence of one or more glands, (2) inclusion within the thyroid or thymus glands, (3) abnormal position and asymmetry of the glands, and (4) unskilled or impatient dissectors.

Each gland may show marked variations in size, shape, weight, and sometimes color. Each may vary from 3 to 15 mm. in length, from 2 to 4 mm. in diameter, and from 0.5 to 2 mm. in thickness. The size of any one body is thought to be dependent, in part, on the total number present, the ratio being an inverse one. Because of the soft, flabby, and yet inelastic consistency of the gland, the shape is easily altered by the pressure of structures.

Pappenheimer and Wilens<sup>3</sup> found that the average weight of the upper glands ranges from 0.027 to 0.032 Gm. each. The lower glands

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were found to be approximately 20 per cent heavier. In females, during active sexual life, the parathyroids have been found to be even an additional 20 per cent heavier.

In infancy and childhood the glands are a light yellowish red, and with increasing age there is a gradual darkening to a yellowish brown or reddish brown color.

The superior pair are more constant in position and usually are found on the posteromedial surface of the thyroid lobes at about the level of the junction of the upper and middle thirds of this structure. The inferior pair are commonly found on the posterior surface of the inferior pole of the thyroid. However, their positions may vary from the angle of the jaw to the anterior mediastinum, and from in front of the thyroid to a position posterior to the esophagus.<sup>4-7</sup>

The blood supply of both upper and lower pairs is received from branches of the inferior thyroid artery. The superior pair may occasionally be supplied by a branch from an anastomosing trunk of the superior and inferior thyroid arteries. The arteries are of the terminal or "end" type.<sup>8</sup>

The nerve supply is furnished by a few, nonmedullated nerves, vasomotor in function, which arise in the middle and inferior ganglions of the cervical sympathetic trunk.<sup>9</sup>

Thus far, there has been no detailed study of the lymphatics.

Prior to 1935 confusion existed as to the types of cells composing the parathyroid glands. In that year, Castleman and Mallory<sup>10</sup> recognized four major cell types with transitional forms. Morgan<sup>11</sup> in 1936 studied the cytology of over 300 normal glands. He also recognized the same four cell types: i.e., the pale principal cell, the dark principal cell, the dark oxyphilic cell, and pale oxyphilic cell. He stated that the pale principal cell is the primary one from which all other types arise in the order just described.

The essentially basophilic pale principal cells comprise the bulk of the gland, and although present throughout life, they decrease relatively in number with advancing age. They are round to polygonal in shape, with a diameter of 7 to 15 microns, with a nucleus measuring 5 to 6 microns. The cytoplasm consists of an irregular network of particles of various sizes. When these particles are stained by the pyronine methyl-green method, they appear light red. Vesiculation is present, and as this increases, the cytoplasmic network is pushed to the periphery. This increases the prominence of the limiting membrane. When vesiculation is extreme, the nucleus appears to be lying free in an empty cell.

The dark principal cells are present in infancy and increase in number relatively with advancing years. They are smaller than the pale variety, the diameter measuring from 6 to 12 microns. The cytoplasmic network is irregularly fragmented and vesiculation is present. The nucleus is small. It measures 3.5 to 5 microns in diameter, is irregular



in shape, contains closely packed chromatin granules, and takes a deeper stain than the nucleus of the pale type.

The dark oxyphil cells are relatively few in number. They measure from 6 to 14 microns in diameter, are polygonal in shape, with oxyphilic cytoplasm almost or entirely filled with granules of a fairly uniform size. The nucleus is similar in appearance to that of the dark principal cell though slightly larger (4 to 5 microns).

The pale oxyphil cells are more numerous than the dark oxyphil cells. They are irregularly polygonal and are very large (9 to 15 microns). The cytoplasm stains reddish pink with hematoxylin and eosin and contains many granular masses. The nucleus is 4 to 6 microns in diameter, is paler than that of the dark oxyphil cell, has a homogeneous appearance, and is usually toward one side of the cell.

In each cellular type, fat and glycogen have been found, but more predominantly so in the principal cells.

The cells frequently appear in rows or columns which are folded on themselves. Acini are found in glands of all ages. The cells lining the alveoli tend to be low columnar or cuboidal and generally are the principal cells. The number of acini and the position within the gland are extremely variable. They usually contain a clear colloid material which stains evenly with eosin. The oxyphil cells tend to appear in groups near the poles and periphery of the gland.

The physiologic significance of each cell type is not known. Since the principal cells are almost the only variety found in infants and young children during the period in which bone formation is most active, Morgan<sup>11</sup> concluded that these cells mostly were responsible for the secretory activity concerned in the role of the parathyroid glands in calcium metabolism.

#### CONSIDERATION OF MALIGNANCIES

Recognition is given to Sandstrom<sup>12</sup> for having first described the parathyroid glands in 1880. From the first description until 1926 the relationships of these glands remained more or less a mystery. In 1926 Mandl<sup>13</sup> proved their importance to the skeletal system by producing alleviation of calcium metabolic abnormalities in a case of osteitis fibrosa cystica by removal of a parathyroid tumor. This finding created new interest in the physiology and pathology of the parathyroids, resulting in a vast amount of literature on these structures.

Between 1880 and 1926, many tumors of the parathyroid glands were reported. In the last decade the number has run into the thousands. An overwhelming majority of these tumors were benign. Malignancies have been reported rarely, only twenty-one being found in the medical literature.

In 1909, Kocher<sup>14, 15</sup> reported eight cases in which the tumor was usually present for years. Three were females; five were males. The

ages ranged from 46 to 61 years. The tumors ranged in size from small nodular "rests" to one 12 by 9 by 9 cm. Two tumors were in the mid-line, four were on the left side, and the position of the other two was not stated. No bony changes were noted. These tumors were usually nodular, fixed, either hard or elastic. Histologically, they were characterized by large transparent cells with sharp red boundaries and the absence of granular eosin red protoplasm but containing varying amounts of glycogen. Presence of this glycogen prompted the name "glycogenous goiters of Kocher." Sarcomatous-like tissue was also present and in some instances even giant cells were found.

In 1909, De Quervain<sup>16</sup> reported a case in which there was invasion of the jugular vein and the sternocleidomastoid muscle, and five months later pulmonary metastasis as well as local recurrence developed. The tumor showed the typical arrangement of the parathyroid gland. The patient was a male, aged 68 years, in whom no bony changes occurred. The tumor was located on the right side of the neck and was 6.5 cm. in diameter.

In 1914, Roffo and Landivar<sup>17</sup> reported a case of a mediastinal tumor adherent to the surrounding structures and which pulsed with the pulsation of the aorta, simulating an aneurysm of the arch of the aorta. However, its volume did not increase with the pulsations. The removed tumor, 10 cm. in diameter, was lobulated and possessed a fibrous capsule which sent many trabeculae into the mass, some of which contained calcium deposits. The sectioned tumor was grayish white, contained many cavities of various size which contained colloidlike material. Other portions showed hemorrhagic areas. Histologically, the tumor tissue was composed of follicles with columns of cylindrical cells containing nuclei in mitosis. Frequently, the proliferated epithelium possessed large vesicular nuclei. In the metastasis which later occurred in the thyroid gland, lungs, and liver, the predominating cells were elongated and polyhedral cells with well-defined limits. The patient was a male, aged 60 years, in whom there were no bony changes. The tumor was on the left side at the lower pole of the thyroid.

In 1923, Fasiani<sup>18</sup> reported a case of a tumor 10 cm. in diameter, elastic and movable, nodular, and containing many cavities and solid nodules. Tumor tissue corresponded to that of the parathyroid gland. Mitosis and invasion of the thyroid gland were marked. The patient was a female, aged 65 years, with no evidence of bony changes. The tumor was situated in the left side of her neck.

In 1925, Ferrero and Sacerdate<sup>19</sup> reported a case of a tumor developing in the femur which was fractured by the examining physician. This tumor possessed the structure of the parathyroid gland. One month after the fracture of the femur, an apparently benign metastasis appeared in the right temporal bone. A small tumor, which had been

present in the right side of the neck for fourteen years, was found. The patient was a female (age not stated) with no other bony changes than that described.

In 1927, Alessandri<sup>20</sup> reported a case of combined thyroid and parathyroid tumor of the right humerus with metastasis to the shoulder (previous history of two injuries to the shoulder). Although no tumor was found in the neck, the tissue simulated parathyroid gland structure. The cells were neatly defined, largely polyhedral, with light-staining protoplasm, situated in a stroma of thin connective tissue with numerous broad and varicosed capillaries. The central, well-eosin-stained nuclei contained plenty of chromatin. The patient was a male, aged 51 years, with no other bony changes.

In 1929, the tumor observed in a 34-year-old female at the Mayo Clinic by Wellbrock<sup>21</sup> and also Wilder<sup>22</sup> measured 5 by 3.5 by 3 cm. and was situated at the lower pole of the right thyroid gland. It was nodular, fluctuating, and semielastic in consistency and clothed in a fibrous capsule. On section, it consisted of four distinct encapsulated nodules composed of yellowish brown, fairly firm, and reddish blue spongy tissue, containing several cavities varying in size and filled with amber-colored fluid. Microscopically, the neoplastic portion of the nodules was composed of large, clear cells with poorly staining cytoplasm, polygonal in shape and containing variable sized nuclei with deeply staining, coarsely granular chromatin material. There were also bandlike masses of more deeply staining cells in which the cellular limits could not be seen very clearly. Many mitotic figures were present.

This case, in addition, showed local and diffuse decalcification of the bones with hyperparathyroidism.

In 1929, also, Guy<sup>23</sup> reported a case in a female, aged 29 years, in whom the tumor was situated behind and below the left lobe of the thyroid and measured 8 by 6 by 4 cm. The cut surface revealed a cortical yellowish portion and a grayish medullary gelatinous portion. Histologically, the tumor consisted of the clear type of cells arranged in columns. No oxyphilic cells were seen. Biopsy was done eleven months later on three recurring nodules on the neck. In this latter tissue, there was a marked variation in the size, shape, and chromatin content of the cells. Mitotic figures were abundant. The palisade arrangement was lost, and the cells grew in great confusion. They were seen infiltrating the surrounding soft tissues and growing into the endothelium-lined spaces in which they were found in masses.

In 1931, Toland<sup>24</sup> reported a case in a female, aged 60 years, in whom the tumor was found at the upper pole of the right lobe of the thyroid and densely adherent to the surrounding muscles. No histologic report accompanied the case description, but Hall,<sup>25</sup> two years later, studied the slides and found it to be adenocarcinoma of the parathyroid. Irregular, atypical cells of various sizes and shapes possessing large hyper-

chromatic nuclei were seen. The cells were arranged in a haphazard fashion. Mitotic figures were present but in some sections hard to distinguish.

In 1932, Price and Mowat<sup>25</sup> reported a case in a 49-year-old male in whom the tumor was found behind the angle of the left jaw. The mass was the size and shape of a hen's egg, and because it appeared at the angle of the jaw, they believed it to have developed from a parathyroid rest. Because of the infiltrative invasion of the surrounding tissues, including the internal carotid artery, only portions of the neoplasm could be removed, and radium therapy was instituted. Histologic examination of one part of the tissue revealed normal appearing parathyroid cells in palisade formation with scattered areas of alveolar formation. Sections from other parts of the mass showed a somewhat similar arrangement, but the cells were large and polyhedral in shape with large nucleoli and marked vacuolization of the cytoplasm. Many areas of necrosis were present.

In 1933 Sainton and Millot<sup>26</sup> reported a case (the age and the sex of the patient were not given) of malignant adenoma in a case of hyperparathyroidism with osteitis fibrosa cystica. The tumor was situated in the left lower parathyroid gland, was about the size of a "green walnut," was covered by a dense fibrous capsule, and invaded the surrounding tissue. Microscopically, the variable sized, dedifferentiated tumor cells were round or polygonal. The cytoplasm was abundant, with finely granular character, and stained eosinophilic. Borders of the cells were indistinct. The pyknotic nuclei were centrally placed, were very basophilic, with chromatin divided in lumps. Mitosis and cellular necrosis were present.

In 1934 the case of Hall and Chaffin<sup>27</sup> was reported. The patient was a male, 46 years of age, who exhibited no bony changes. The tumor, 11 by 8 by 5 cm., was located in close proximity to the left lobe of the thyroid, and invaded the band muscles of the neck. Sections from various parts of the tumor showed anastomosing cords and columns of atypical epithelial cells which had invaded the surrounding muscle tissue in places. In other parts the tumor was limited by a fibrous capsule. Scattered fibrous tissue bands crossed the tumor. In a number of places large cell masses appeared in which the alveolar arrangement was not very evident. The nuclei of the epithelial cells were round or oval, vesicular, and moderately deep staining. They contained one large and often one or two small nucleoli. The nuclei were variable in size; some of them appeared quite large. Occasional mitosis was seen. The cells were polygonal in shape with abundant, finely granular, moderately eosinophilic cytoplasm. Some groups of cells had clear cytoplasm. Other groups of cells, which had a tendency to be elongated or fusiform, had hyperchromatic nuclei and more deeply staining cytoplasm. These cells had a loose, nondescript arrangement and appeared to be distinctly atypical. In several places, masses of tumor cells were seen in the small

and medium-sized veins of the stroma. Other cell groups about the border of the tumor appeared to be in the lymphatic vessels.

In 1936 Snell<sup>28</sup> reported a case seen at the Mayo Clinic in a male 47 years of age. The tumor was found at the lower pole of the right lobe of the thyroid gland, behind the trachea, and slightly under the sternum. It measured 6 by 6 by 5 cm., was smooth and covered with a plexus of veins. No histologic description was given. The diagnosis rendered by the pathologist was carcinoma of the parathyroid gland, Grade I.

This case also exhibited hyperparathyroidism with miliary osteoporosis.

In 1938 Armstrong<sup>29</sup> reported a case in a 71-year-old female, the tumor being situated on the right side of the neck. It measured 11 by 11 by 4 cm., was stony hard, reddish brown, and covered with a dense fibrous capsule. It was adherent to the internal jugular vein and the sternocleidomastoid muscle.

The cells were arranged in loosely packed masses and long columns. They were round and oval, large in size, with abundant acidophilic cytoplasm containing clear vacuoles. The nuclei were well stained. Mitosis was not reported. The diagnosis was carcinoma.

#### REPORT OF CASE

J. A. S., white male, aged 38 years, a machinist, was admitted to the U. S. Marine Hospital, on Oct. 17, 1936, with the chief complaint of "broken legs, arm and shoulder." While attempting to climb up a flight of stairs, his legs became weaker than usual; he could no longer stand up and fell. He did not fall very far, only about the height of four ordinary steps. However, he was unable to get up unassisted.

For one and one half years previous to admission the patient had been annoyed by what was thought by his family to be arthritis, yet the joints of the body were not necessarily affected. At times during this period his ankles and knees had become terribly painful and extremely swollen. In addition, pain was experienced in the shoulders, particularly the right. Occasionally he experienced "muscular pains" most marked in the legs, which he described as "sharp, shooting" pains. Polyuria had been present for years.

Since onset of the pains, he had become slowly, progressively weaker, was unable to do the work he had previously done, and had lost eighteen pounds of weight. He had not noticed any decrease in height. On the day before admission, he experienced a sore throat. For the first time he noticed a small lump in his neck just above the sternal end of the left clavicle.

Physical examination revealed a poorly developed, poorly nourished 38 year old, pale, white male, who appeared much younger than his age. In the neck just above the sternal end of the left clavicle was a mass which was hard, firm, nodular, and unattached to the skin. Its size approximated that of an English walnut and was in the region of the left lobe of the thyroid gland. The teeth were very carious. The heart exhibited a soft, blowing diastolic murmur, best heard at the apex. The point of maximal impulse was in the sixth left interspace 2 cm. beyond the mid clavicular line. The pulmonary second sound was greater than the aortic second sound. Blood pressure was 170/100. The blood vessels were normal. Mucous membranes were pale and possessed a yellowish color.

Urinalysis showed a specific gravity of 1.009 and a trace of albumin. Kahn test was negative. Red cell count, 4,200,000, white cell count, 18,000; hemoglobin 65 per cent. Differential smear revealed neutrophils, 80 per cent; small mono-

nucleais, 19 per cent; and transitionals, 1 per cent. Blood sugar was 80 mg. per 100 c.c. of blood. Blood calcium was 14.7 and blood phosphorus 3.4 mg. per 100 c.c. of blood. Phenolsulphonphthalein test totaled 20 per cent after two hours. Mosenthal concentration test showed greatest specific gravity to be 1.007. Test for Bence-Jones bodies was negative. Electrocardiogram revealed only sinus tachycardia. Roentgenologic findings were as follows: "The right humerus shows a fracture at the surgical neck with the fragments in good position. The left femur shows a fracture through the middle third with slight posterior displacement of the lower fragment. The right femur shows a fracture of the upper third with the fragments in good position. The bones in this case show an outstanding condition. There is absorption of the calcium from the center of the bones to the cortex. The bones, in areas, show only a shell-like structure remaining, being only slightly more dense than the soft tissues." (Figs. 1 and 2.)

The other bones were x-rayed and "the left humerus, scapulae, clavicles, and, to a lesser extent, the ribs show similar changes to those previously reported in the femurs, pelvis, and right humerus. None of these changes are seen in the skull or the left forearm."



Fig. 1.



Fig. 2.

Fig. 1.—X-ray of left femur on admission showing marked decalcification and a fracture through the middle third.

Fig. 2.—Right humerus with marked demineralization and fracture of the surgical neck. Arrow indicates ring of calcium deposit within tumor.

The fractured members were immobilized by plaster casts. Repeated blood chemistry showed a persistent high calcium and low phosphorus. Therefore, on Nov. 16, 1936, an exploratory operation of the neck was performed under local (1 per cent novocain) anesthesia. A hard, nodular tumor (Fig. 3) was found in the region of the left lobe of the thyroid gland, densely adherent to this gland, but not actually a part of it. The mass measured 5 by 3 by 2 cm., was reddish brown in color, and possessed a ring of calcium at one end. This calcified ring was previously seen in the x-ray film taken primarily to show the condition of the right humerus and ribs (Fig. 2). X rays of the removed mass showed the calcification within the mass (Fig. 4).

The specimen was sent to the National Institute of Health, Washington, D. C., for histopathologic study. The report is as follows: "Left parathyroid has a thick, densely fibrous capsule and trabeculae [Fig. 5], which show patches of

lymphocyte and plasma cell infiltration, an occasional small area of calcification and few foreign body granulomata, in which large angular spaces occur, presumably cholesterol clefts. The parenchyma [Fig. 6] is formed of large and small sheets, nests, and columns of cells enclosed by or embedded in the dense fibrous tissue. Tumor cells are polygonal and medium to large in size. They have much reticulo-granular oxyphilic to amphophilic cytoplasm with distinct cell borders. Nuclei are medium to large in size, vesicular, usually centrally located, commonly have one or more large nucleoli, and are moderately and occasionally marked hyperchromatic [Fig. 7]. Few cells are binucleate and rarely a multinuclear cell is seen. Few mitoses are present. One medium sized venous channel shows invasion of its wall by an adjacent tumor nodule [Fig. 8]. In many areas small, poorly circumscribed cell nests occur, and few of these show infiltration of the surrounding fibrous tissue. The larger cell sheets occasionally show focal coagulation or karyorrhectic necrosis.

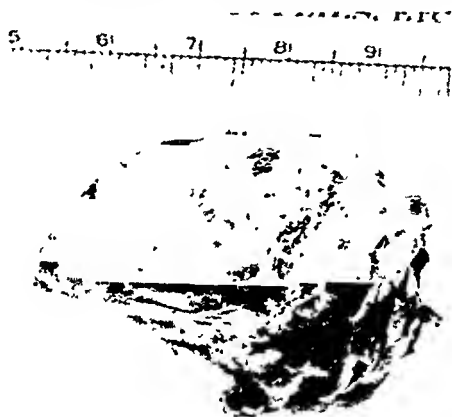


Fig. 3.—Reddish brown, hard, nodular tumor removed at operation.

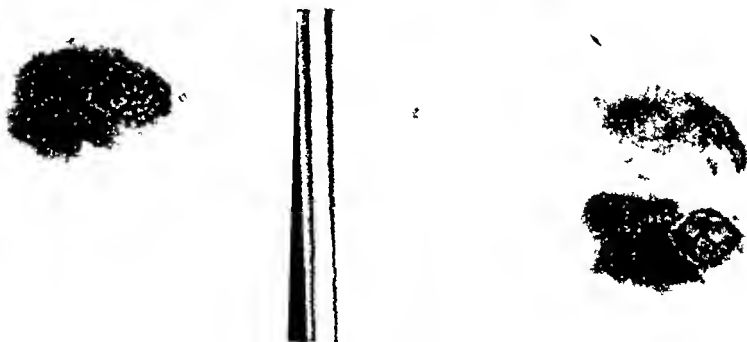


Fig. 4.—X-rays of tumor mass removed at operation, showing within the growth the calcium deposit noted in Fig. 2.

"Little striated muscle and less thyroid tissue is adherent to capsule.

"Diagnosis: Adenoma of parathyroid (malignant?)."

Immediately after the left parathyroid gland was removed, the blood calcium fell rapidly with an irregular level of blood phosphorus (Fig. 9). Large doses of calcium salts (gr. 225 daily), vitamin D, and a high calcium diet were given. Although the blood calcium fell below the established critical level, the patient showed no signs of tetany. As the blood calcium reached the normal level, the calcium therapy was less intensive.



Fig. 5.—Low-power view of tumor showing peripheral layer of fibrous tissue continuous with the lobulating trabeculae ( $\times 16$ ).



Fig. 6.—Photonucleograph showing general tumor structure ( $\times 128$ ).



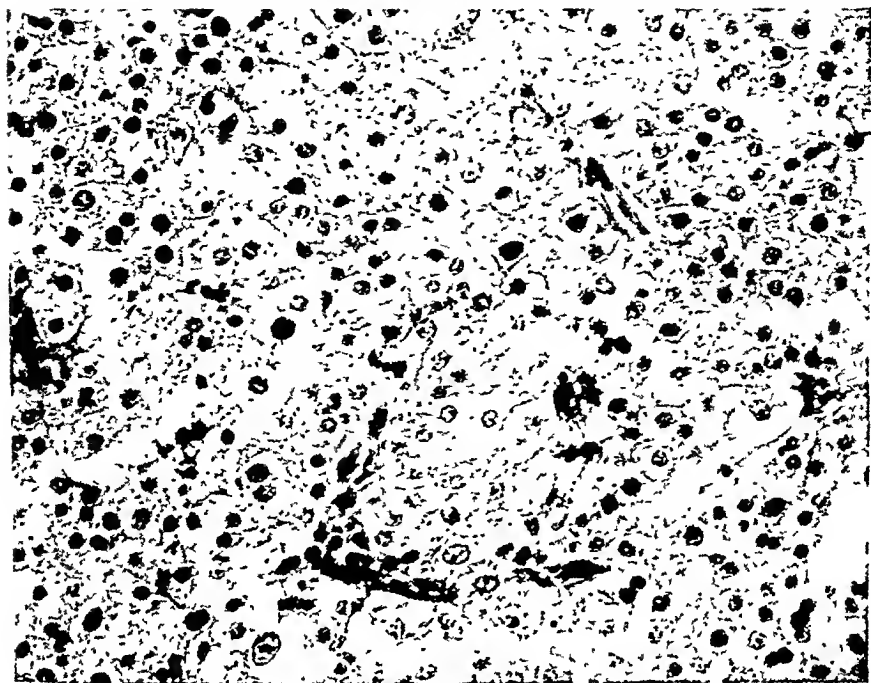


Fig. 7.—High-power view, showing variation in nuclear size, nuclear hyperchromasia, granular cytoplasm, and distinct cytoplasmic borders ( $\times 500$ )



Fig. 8.—Tumor mass invading wall of wide vascular channel ( $\times 210$ ).

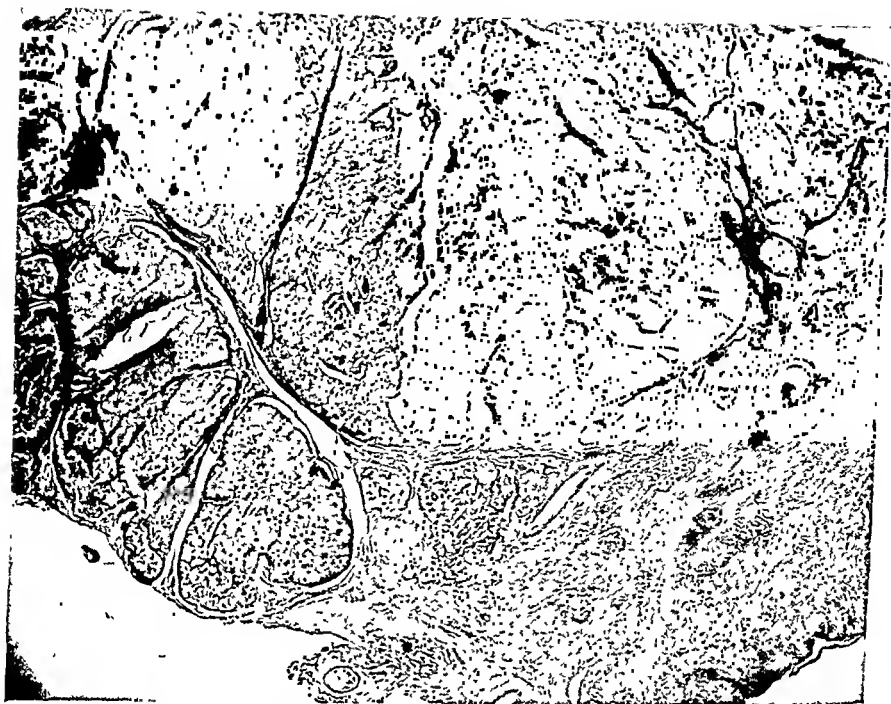


Fig. 5.—Low-power view of tumor showing peripheral layer of fibrous tissue continuous with the lobulating trabeculae ( $\times 16$ ).



Fig. 6.—Photomicrograph showing general tumor structure ( $\times 128$ ).

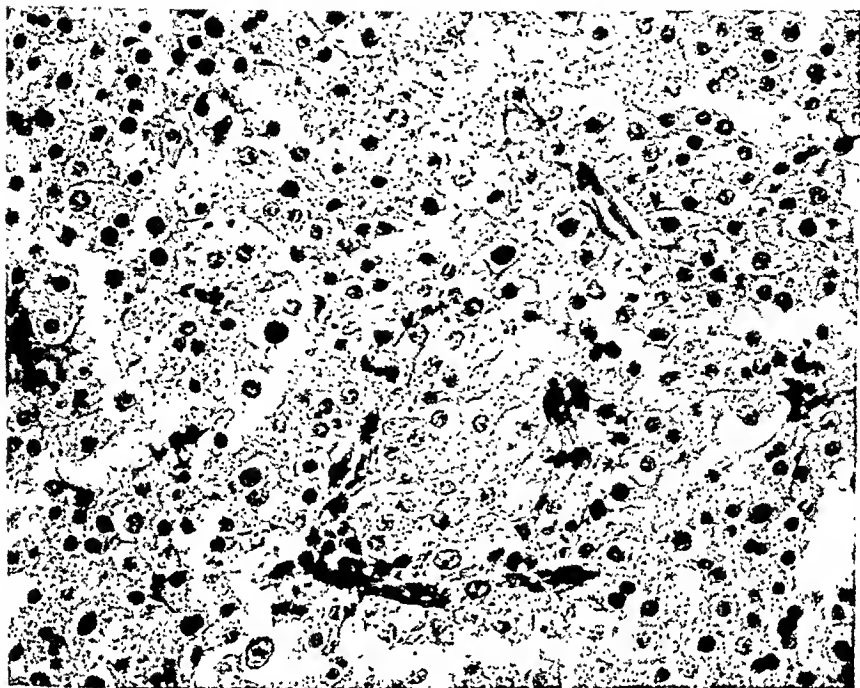


Fig. 7.—High-power view, showing variation in nuclear size, nuclear hyperchromasia, granular cytoplasm, and distinct cytoplasmic borders ( $\times 500$ ).



Fig. 8.—Tumor mass invading wall of wide vascular channel ( $\times 210$ ).

The patient's condition generally and as to the calcium content of the bones improved slowly until January, 1937. At this time he again began to experience some of his original complaints, such as weakness and pains in the muscles, and hoarseness increased. The blood calcium rose above the normal, and the blood phosphorus was lowered. No cause could be found for this until the middle of July, 1937, when an enlargement of a cervical gland on the left side of the neck was noticed.

This gland was removed at once and sent to the National Institute of Health for study. The report is as follows: "The 8 by 11 mm. tumor mass is enclosed in a dense layer of scar tissue, which is thicker where it gives rise to trabeculae which completely or incompletely lobulate the tumor. This fibrous tissue shows patches of lymphocytes and little scattered, free and phagocytosed hemosiderin.

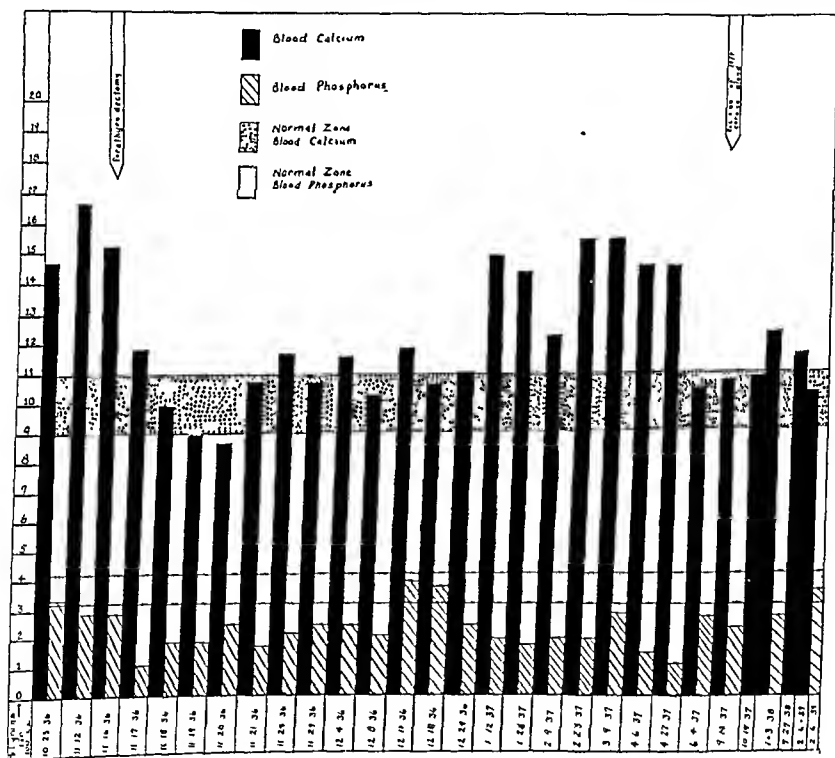


Fig. 9.—Blood calcium and phosphorus levels during course of two and one-half years' observation.

Parenchyma is formed of large and small sheets and strands of coherent tumor cells which are polygonal, medium to large in size, and have distinct cytoplasmic margins. Cell nuclei are medium to large in size, round, vesicular, and moderately hyperchromatic, and show one or more distinct, usually large nucleoli. Few mitoses are seen. Cell cytoplasm is ample, granular, and oxyphilic, less often amphophilic. Tumor cells immediately surrounding blood vessels are usually larger than elsewhere, are roughly columnar and show irregular radial arrangement. Few cell sheets show focal coagulation necrosis. A small collapsed cyst present in peripheral fibrous layer is lined by bud-like masses of vascular granulation tissue. In some of the vascular spaces, there are masses of tumor cells, some apparently lying free while others are loosely adherent to wall [Fig. 10]. In some of these vessels there is little blood. Occasionally a tumor mass occurs in a larger vessel.



Fig 10—Section from metastasis to left cervical lymph node showing intravascular tumor mass ( $\times 515$ )



Fig 11

Fig 11—Right humerus with fracture of surgical neck healed. Decalcification throughout bone is less marked (Sept 10, 1937).



Fig 12

Fig 12—Right and left femurs with fractures healed. Density of bones increased (Sept 10, 1937)

"A small lymph node loosely attached to tumor shows moderate sinus endothelial proliferation. A second detached node shows in addition a vascular space filled with tumor cells.

"Diagnosis: Malignant adenoma of parathyroid gland, metastatic."

After removal of the metastatic gland, the blood chemistry returned to normal levels (Fig. 9). The fractures healed rapidly, and some of the cystic areas of the bones became more densely filled with calcium (Figs. 11 and 12). The patient was discharged Nov. 1, 1937. At this time he was able to walk with crutches.

On Jan. 3, 1938, the patient was readmitted for check. His weight was 135 pounds. Clinically, union appeared firm at site of fractures; some deformity was present at the site of fractures; both knee joints were slightly swollen; urine showed 1 plus albumin; Kline exclusion test was negative. P. S. P. test showed 20 per cent function in fifteen minutes, 30 per cent in one hour. Blood calcium was 12.5 mg. per 100 c.c. of blood. Blood phosphorus was 2.7 mg. per 100 c.c. of blood. *X-ray Report*: "The cystic changes in the femurs are still quite noticeable but there is evidence of considerable recalcification present. The old fractures are firmly united and appear quite strong. There are no cystic changes in the fibula or tibia of either leg. The cystic changes in the humerus of each arm are quite outstanding. Almost the entire shaft of the humerus is involved. The middle third of the right humerus shows the greatest changes observed in that bone. The changes in the right humerus are less prominent now than previously. The left humerus does not show any improvement."

The patient was discharged on Jan. 15, 1938, to return in six months. Patient was readmitted July 27, 1938. His chief complaint was pain in his arm and inability to use his left arm. Otherwise, his general condition had been good since the last admission. He could use his right arm freely. His weight was 132½ pounds. Blood pressure was 170/110. Physical examination was practically the same. Right knee at this time had considerable grating on movement; the motion of the left shoulder joint was limited in all directions and appeared to be tender over the middle portion of the humerus where there appeared to be fusiform swelling. Urine showed 3 plus albumin; Kline and Eagle tests negative; blood calcium, 11.7 mg. per 100 c.c. of blood. *X-ray Report, July 30, 1938*: "The left humerus, scapula and outer end of the left clavicle show the same general condition as was previously observed in November, 1937, except that the radiolucent areas are more clearly defined now and somewhat larger than they were at that time. There has been no suggestion of recalcification and there are new areas developed in the lower end of the humerus just above the epicondyle. The main shaft of the humerus is now little more than a shell of the normal bone. There is no break however in the external surface of the bone at any place. These changes were thought to be originally a result of a pathology of the parathyroid. In view of the malignant condition found in the adenoma removed from the region of the parathyroid and also since there had been no recalcification of the cystic-like areas found throughout the general skeleton, these changes are quite interesting and unusual. Biopsy should prove most interesting."

*X-ray Report on Aug. 2, 1938*: "The cystic areas in the femurs are not as prominent as when previously observed over a year ago [Fig. 13]. The tibias appear essentially normal. Each humerus shows gross cystic areas some of which are so great as to leave merely a shell of the bone shaft [Fig. 14]. The left is the greater involved and there are two new cystic areas in the lower section of the left humerus which has developed in the past year. These are quite circumscribed in outline. The bone changes in this case are most unusual, especially in view of the malignant nature of the tumor removed from the region of the parathyroid gland."

At this time, the patient was able to walk without the aid of crutches, hoarseness in his voice was improved, and his chief complaint was pain in the left shoulder

and arm. (No report of the phosphorus content of the blood at this time.) He was discharged on Aug. 8, 1938, to return in six months for check.

Patient was readmitted Feb. 6, 1939, for check. On this admission, he did not offer any complaint. His general appearance was good. His weight was 132 pounds and blood pressure was 185/108. On examination and special examination of the neck, there was no evidence of any local recurrence. His blood calcium was 10.5 mg. per 100 c.c. of blood and phosphorus was 3.7 mg. per 100 c.c. of blood. *X-ray Report:* "The femur shows all the old fractures firmly united and greater density than at previous examinations. The gross cystic changes previously observed in the humerus of each arm appear essentially the same. There are large cystic areas in the shaft of both bones. In some areas, there is little more than shell of the bone remaining. The fracture of the humerus is firmly united."



Fig. 13.

Fig. 14.

Fig. 13.—Femurs well healed, twenty-two months after admission.

Fig. 14.—Right and left humerus twenty-two months after admission showing very little improvement in the right. Two new cystic areas are seen at the lower end of the left humerus.

#### COMMENT

Including the case presented herein, there have been reported 22 cases of malignant tumors of the parathyroid glands. Nine of these have been in females and 12 in males. The sex of 1 patient was not noted. The youngest and oldest patients were 29 and 71 years of age, respectively. Three cases were patients between 29 and 45 years of age, and 17 were in patients from 45 to 71 years of age. Two reports omitted the age of the patients. The tumor was situated on the left side of the neck in 10 cases, on the right in 6, in the midline in 2, and in 4 the sites were not listed. The sizes of the tumors ranged from small nodular rests to 12 by 9 by 9 cm. In 4 cases bony decalcification was present. The favorite sites of metastasis were the muscles of the shoulder and neck, cervical lymph nodes, trachea, and lungs. Recurrence at the original site occurred in 2 instances.

Grossly, most of the tumors were densely covered by a thick fibrous connective tissue capsule which occasionally was densely adherent to contiguous muscle. Most of the tumors were nodular and lobulated. Their consistency varied greatly. Some were stony hard, some were firm but elastic and possessed fluctuant areas. Calcified areas were present in a few specimens. The color ranged from a bluish gray to reddish brown.

On cut sections, the tumors appeared yellowish gray, yellowish brown, or some intermediate color. From the capsule, trabeculae of fibrous connective tissue were found to course through the tumorous mass completely or incompletely to lobulate the neoplasm. In many specimens cystic areas with thin walls of fibrous connective tissue were noted. These cysts were filled with an amber-colored serous fluid or amber colloidlike material. Occasionally they contained blood. In 1 case the cyst was encircled completely by a ring of calcium deposit (Fig. 4), which was visible in an x-ray film taken before the tumor was removed from the patient (Fig. 2). In some nodules of the tumors, necrotic centers were found.

Microscopically, all the tumors reported exhibited definitely the structure of the parathyroid glands. The stroma was usually made up of thin connective tissue fibers. At times the supportive network consisted of thick fibrous bands with lymphocytic or lymphoidlike cell infiltration. Occasionally the stroma was formed almost completely by capillary vessels.

The parenchyma consisted of compact, anastomosing strands of cells in between which were found vesiclelike spaces, thereby giving the effect of palisades. Such order was not necessarily always present, as Guy<sup>23</sup> found the cells growing in "lawless profusion." Varying sizes of cell sheets or nests were seen which were or were not enclosed by fibrous tissue.

Although the individual cells were predominantly of the large, clear variety (principal cells), several cases showed a predominance of oxyphilic cells. Others possessed approximately equal numbers of each type. The boundaries of the cells were distinct, encircling an abundance of cytoplasm, which in the clear type was poorly stained. In the oxyphilic cells the cytoplasm was finely granular and moderately or markedly eosinophilic. Although the most predominant cell shape was polygonal, many were spheroidal or enboidal. The nuclei were round or ovoid, usually centrally placed, either vesicular or homogeneous, and possessed a fairly abundant amount of chromatin material. Their size varied considerably, but usually they were very large. Wellbrock<sup>21</sup> found the largest nuclei to be approximately seven times the size of a normal nucleus. Usually they contained one or two fairly deeply staining nucleoli. The number of mitotic figures was not constant. In some cases they were seen only occasionally, while in others they were present abundantly.



In all cases in which metastases occurred, the metastatic growth showed the same histopathologic picture as the primary tumor, with a tendency to possess characteristics of a greater degree of malignancy. Additionally, as seen in our case, the metastasis is apparently quite capable of exerting the same influence on the metabolism of calcium as that held by the normal gland, but this influence is without restraint.

There are no definitely dependable characteristics by which a tumor of the parathyroids might be diagnosed clinically as benign or malignant. For the most part, malignant tumors are usually larger. Hall and Chaffin<sup>27</sup> in 1934 noted that over 50 per cent of the benign tumors recorded in literature had shown decalcification of the bones to some degree, while only demineralization had been seen in only 1 case<sup>21</sup> of the 18 malignant tumors which they had reviewed. They concluded, therefore, that bony changes were not so likely to be present in patients with parathyroid malignancies, and if they were, the chances of the tumor's being benign were considerably increased. With this report, 4 cases of malignancy of the parathyroid glands have been noted in which demineralization of the skeleton occurred.<sup>21, 26, 28</sup> In only 1 case<sup>28</sup> were the bony alterations described as a diffuse milary osteoporosis. The other 3 possessed large cystic areas, particularly present in the long bones and pelvis. One should bear in mind that procrastination should not be courted in removing a parathyroid tumor because bony changes are present. It might still be a malignant affair!

#### SUMMARY

1. A brief description of normal parathyroid glands is presented.
2. Twenty-one cases of malignant parathyroid tumors found in the literature are reviewed briefly.
3. An additional case of parathyroid malignancy is reported. The tumor was situated in the left side of the neck and metastasized to a left cervical lymph node. The cells comprising the neoplasm were of a variable large size, mostly polygonal, and contained oxyphilic cytoplasm. The vesicular nuclei were fairly large, moderately to markedly hyperchromatic, and contained one or two hyperchromatic nucleoli. Few mitoses were seen. The cells were arranged in sheets, nests, and columns enclosed by fibrous tissue.
4. Decalcification of the bones was present and so marked that multiple fractures were sustained by the patient from an otherwise insignificant fall.
5. Three years after removal of the original tumor, the patient is alive and well. The fractures are well healed and moderate recalcification of the bones has occurred.\*

\*Since this paper originally was written, the patient was seen again in September, 1941. At that time his general condition was excellent and he felt much better than at any time since his original hospital admission in October, 1936. His blood calcium was 10.8 mg., and blood phosphorus, 2.8 mg. per 100 c.c. of blood. X-rays of both humeri show that all of the cystic areas have nearly filled in with calcium.

The authors are indebted to Dr. J. H. R. Booth, U. S. Marine Hospital, Baltimore, Md., for his splendid cooperation in the roentgenologic work involved in the case reported.

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## FASCIAL RECONSTRUCTION OF THE TIBIAL COLLATERAL LIGAMENT

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THE FUNCTION of the knee joint is, to a large degree, determined by the anatomical integrity of its ligamentous apparatus. Because of this, considerable effort has been expended in an attempt to establish the exact significance of each of its component parts in the mechanism of the knee as a physiologic unit. Despite the extensive literature on this subject, opinion is far from being unanimous. This may be attributed to the fact that some of the conclusions have been gained from clinical observation, others from anatomical or experimental studies. Though this information cannot and should not be neglected, it must not be forgotten that such data may not be directly applicable to the problems presented by clinical surgery.

The primary interest of the orthopedic surgeon is not the didactic determination of the function of each of the ligaments, but rather the evaluation of their relative significance to the knee as a whole. Information on this question can best be obtained by a study of the results of surgical efforts at repair of damage to definitely determined ligamentous structures. From the fact that anatomically the crucial ligaments appeared to be most important, the earlier surgical efforts were expended on the repair of these structures. These early trials were only partly successful, and a marked step forward was made when the fascial reconstruction, originally devised by Grekow<sup>2</sup> and later elaborated by Hey Groves,<sup>3</sup> was introduced. But even this did not seem to give complete satisfaction until a procedure for the repair of the tibial collateral ligament was added.<sup>4, 5</sup> Since then a number of different methods of fascial repair of this ligament have been devised by Campbell, Carrel, Cubbins, and others.<sup>1</sup> An ever-growing experience seems to indicate that the repair of the tibial collateral ligament is the essential step in the operative correction of the instability which results from loss of the normal ligaments of the knee joint.

In an earlier communication<sup>6</sup> I expressed the opinion, concurred in by others, that injury to one or both of the crucial ligaments was not incompatible with good knee function, but that permanent damage to the tibial collateral was definitely disabling. The lapse of time has not altered this opinion. On the contrary, it has even led to the firm conviction that in the majority of cases injuries to the crucial ligaments cannot be diagnosed with any clinical assurance unless they are associated with injury to the tibial collateral ligament. The so-called

"drawer" or "rocker" sign of De Rocher, which has been considered pathognomonic of crucial ligament injuries, has been elicited usually in those cases in which there has been concomitant injury to the collateral ligament and cannot commonly be elicited if this ligament be intact.

Where this sign has not been present, crucial ligament injuries frequently have led to transitory locking of the knee and have simulated the clinical picture of torn or displaced menisci. Under this mistaken diagnosis, arthrotomy of the knee has repeatedly been performed. In the first few cases in which only a tearing of the anterior crucial ligament was found, the extensive Hey Grove reconstruction operation did not seem warranted by the relatively minor clinical disability. Since the torn ligament appeared to be acting principally as a mechanical block, it was excised. The excellent recovery of these patients justified the procedure, and in consequence, the torn anterior, and occasionally even both torn crucial, ligaments, have been excised without any serious results in those cases in which no evidence of injury to the medial ligament could be elicited. Where both the crucial and collateral ligaments have been injured, repair of the tibial ligament alone has been sufficient to restore an excellent functional capacity to the unstable knee.

If cases in which successful reconstruction of the tibial collateral ligament alone be compared with similar cases in which both the crucial and tibial collateral ligaments were satisfactorily repaired, it will be found that the results, both anatomically and functionally considered, are quite similar. Complete restitution to the normal is an almost unattainable ideal. For the patient, and consequently for the surgeon, it is the functional rehabilitation and not the anatomical restoration that is of primary moment. In this respect the more complicated crucial ligament reconstruction does not seem to have justified itself, while the importance of the tibial collateral ligament repair cannot be denied. The reestablishment of the integrity of this ligament is fundamental if a successful outcome of the surgical procedure is to be expected.

In general, this opinion coincides with that of Mauek,<sup>7</sup> who described an operative procedure on the tibial collateral ligament which served "to remedy the instability of the knee, due to injuries of the internal, lateral, and crucial ligaments." This procedure is based on the belief "that the instability was due to laxity of the medial ligament, rather than to weakness of the structure, and if weakness existed, it was in that part of the ligament adjacent to the tibial head—that portion which was healed by fibrous tissue."

Though it is generally believed that the tibial attachment is the most frequent site of rupture, the evidence on this matter is by no means overwhelmingly convincing. Mauek expressed the opinion "that the application of force which abducts and externally rotates the tibia on

the femur, with the knee slightly flexed (the position in which most injuries to the medial collateral ligament take place) practically always tears the ligaments away from the head of the tibia and the anterior fibers of the ligament suffer the greatest damage." Jones and Lovett<sup>5</sup> state that "clinically, it is the lower attachment of this ligament which usually gives way" and that in a sprained knee "the short, deep fibers of the ligament are injured most often at their attachment to the tibia." However, in the same discussion, they note that "in connection with injuries to the internal, lateral ligament, it is not uncommon to meet with a sprain fracture, which occurs most often where the ligament is torn from the femur, carrying with it a small flake of bone. A similar fracture also occurs when the deep fibers are torn from the upper margin of the tibia." They observe further that "when the leg was forcibly abducted on the cadaver, Tenney found that the internal lateral ligament tore away from its femoral attachment."

Though no accurate estimate of the relative frequency of tearing of the collateral ligament at one or another part can be made, it seems to be incontrovertible that the ligament may and does tear at any point in its continuity. In this regard, the arthrographic observations of Lindblom<sup>6</sup> are extremely important. He observed a group of eighteen cases with recent lesions. "Pararticular leakage through a capsular rupture was seen above the meniscus in three cases and below it in two cases. In all cases of leakage about the meniscus, a rupture was found at the superior attachment of the ligament."

This contradiction in the observed results is one which can only be resolved by actual observation of the fact in living patients. Clinical experience would seem to indicate that though the medial ligament may tear away from its tibial attachment, this is not the invariable or necessary site of rupture. In those cases of lateral instability in which the roentgenogram discloses a fracture in the region of the femoral epicondyle, rupture at the femoral attachment of the medial collateral ligament is generally conceded. An increasing fund of information concerning sport accidents has established the fact that the sprained knee of the skier is so constantly associated with a tender area over the femoral attachment of the ligament that this point has been specifically designated the "ski point." Among football players, too, this area of tenderness is characteristic and is considered as indicating a partial tear of the medial ligament. Unfortunately, actual observations as to the site of rupture of the collateral ligament are not as numerous as could be desired. In the fresh cases, surgical intervention is not justified because of the excellent results obtained by adequate, conservative therapy. In the older cases, it is only with difficulty that the site or even the probability of the rupture can be accurately determined because of scar tissue replacement. It is particularly in regard to this point that the following cases are of interest.

CASE 1.—A. C., colored female, aged 38 years, was admitted to the Hospital for Joint Diseases on Oct. 18, 1938. She stated that while roller skating three years before she had fallen on her flexed and internally twisted right leg. The knee became swollen and painful. Extension was not blocked, but flexion beyond 90° was limited by pain. The patient was advised to make hot applications to the knee and in the course of several weeks the swelling disappeared. She remained well until about three weeks before her admission, when she slipped and again injured her knee in the same manner as previously. One week later she fell upon her hyperflexed knee and came to the hospital, complaining of stiffness and pain. She noted that after her fall the knee felt unstable, and it was necessary to steady the knee with her hand while extending the leg. During the act of extension she noted a snapping sensation along the inner aspect of the knee.



Fig. 1.—Roentgenogram showing nodule on inner aspect of knee.

Examination disclosed a marked swelling of the knee. There was a point of tenderness along the anterior margin of the medial collateral ligament, slightly above the level of the knee joint. This pain was markedly exacerbated by attempts at abduction of the leg on the thigh, but no abnormal lateral mobility could be elicited. The "rocker" sign was negative. Flexion could be performed to 15°. At this point the patient complained of increased pain. Extension was associated

with a clicking noise but was possible to 180° without locking. Roentgenogram (Fig. 1) was reported as showing a "cortical avulsion fracture of the internal femoral condyle, with separation of a small shell-like fragment of bone."

At operation, performed on Oct. 20, 1938, through an oblique incision, a typical bucket-handle fracture of the meniscus was found and the meniscus was removed. The bony body was then isolated. It was found to be about the size and shape of a grain of puffed rice, attached anteriorly to the articular aspect of the internal collateral ligament. There was apparently an articular facet. This mass was excised with uneventful recovery of the patient.

The pathologist reported that this nodule was a "flat, osseous fragment, with a narrow cartilaginous cap, which is found to be modified cartilage."

The fact that this small fragment of bone was attached to the anterior edge of the collateral ligament, with its modified cartilage facing into the joint, seems to indicate that the cartilage was not torn away from a previously existing articular surface but represented a metamorphosis of scar tissue under the stress of constant motion. The nature of the injury, the symptoms immediately noted, the concomitant cartilage injury, and the location of the bony nodule, all tend to confirm the belief that this mass represented the healing stage of a partial tear of the anterior portion of the ligament just above the joint line.

This was exactly the site of the rupture found in a patient upon whom the opportunity of operating within a week of his injury was offered.

CASE 2.—R. G., male, aged 25 years, was first seen on May 1, 1935, five days after he had injured his left knee by jumping over a hedge. He stated that in landing his left knee bent backward and sideways. Though he was "able to get up and walk about, his knee felt very weak and shaky." On walking, he noted that his knee locked and since that time it has repeatedly locked, with the knee in flexion. Examination disclosed that the knee could be extended to about 60° and flexed to 90°. There was marked effusion into the knee joint. There was definite tenderness over the femoral attachment of the tibial collateral ligament and over the fibular attachment of the fibular collateral ligament. In extension there was a marked increase in lateral mobility of the knee. Even when standing the patient was able to dislocate the femur backward on the tibia. In the seated position, with the knee flexed, there was a marked increase in anteroposterior mobility of the lower end of the femur. It was apparent that this patient had suffered a serious derangement of the ligamentous apparatus of the knee, involving both the crucial and collateral ligaments. Because of the symptom of locking, which was presumed to be due to concomitant injury of the semilunar cartilage, immediate operation was advised and performed on the following day.

At operation, a 3-inch medial parapatellar incision was made, and a large amount of bloody fluid was evacuated. The anterior horn of the internal semilunar cartilage was found detached and was removed. The medial semilunar fat pad, which was bruised and hemorrhagic, was removed. The anterior crucial ligament was found torn slightly above its tibial attachment. Since it could not be sutured, the free end was excised. Examination of the external semilunar cartilage revealed an injury to this structure. A small, lateral parapatellar incision was made, and a typical bucket-handle fracture of the external semilunar cartilage was found. The medial detached portion only was excised. Both synovial incisions were then closed,

and the knee was tested for lateral instability. Because of the marked hyperabductability of the knee, the tibial collateral ligament was exposed and carefully examined. A definite transverse tear below the femoral attachment of the tibial collateral ligament was found and was sutured with interrupted heavy chromic catgut stitches. As soon as this ligament was repaired, the abnormal lateral and anteroposterior mobility completely disappeared. The wound was closed in layers, and a plaster of Paris bandage was applied from the thigh to the toes, with the knee in complete extension and the foot in midposition. This plaster was left on for a period of six weeks, and after this physiotherapy was begun. Thereafter the patient left the city, but information from his family physician indicated that a satisfactory restoration of function had been obtained.

While it is true that the tibial collateral ligament may be purposely cut or accidentally injured and yet heal quite soundly, it must be admitted that such healing can only occur by scar tissue formation. It must also be admitted that where instability does occur, a relative lengthening of the ligament at the site of the scar tissue formation must be predicated. It is obvious then that a tear of the tibial collateral ligament at its femoral attachment must be repaired at this site, and a giving way of scar tissue situated in its midportion can be avoided only by a reparative procedure designed to reinforce this weakened area. If these observations be conceded, it becomes apparent that any operation designed to meet all of the contingencies must be one which restores the stabilizing function of the ligament as a whole. This conclusion applies with even greater force to those cases in which the integrity of the ligament has been lost in consequence of infection, arthroplastic or other surgical intervention. It was to meet these indications that the present procedure was evolved by modification of previously existing operations.

Experience with the older procedures has demonstrated that where the fascial graft is left attached at its femoral end, neither the exact course nor the requisite degree of tension can be obtained. Though a slight loss of tension may be compensated for by muscular action, the limitation of motion and the marked loss of tension which follow inaccurate placing of the graft are more serious and may vitiate the result.

Since the essential feature of the present procedure consists in the actual replacement of the tibial collateral ligament by a fascial graft, accurate information as to the exact anatomical attachment, direction, and action of this ligament is indispensable. If the normal internal lateral ligament is carefully examined, it will be found to present an entirely different appearance than is suggested by Gray's classical description. Instead of being a "broad, flat, membranous band," this ligament consists of two parts, anterior and posterior, each of which differs entirely in appearance and action from the other.

The main anterior part extends from the femur to the tibia in the form of a narrow, flattened, white band, almost tendinous, both in its texture and in its oval circumference. It is attached above on a ridge



of the tuberosity of the medial femoral condyle, just below the adductor tubercle. From here the ligament passes downward and slightly forward to its attachment on the tibia. The short, deep fibers to which the semilunar cartilage is fixed are inserted into the tibial tuberosity posteriorly along the line of the capsular attachment. The superficial fibers, about 10 cm. long, continue downward to about the level of the sartorius tendon, before being inserted into the tibia. A small bursa is interposed between the tendon and outer surface of the ligament.

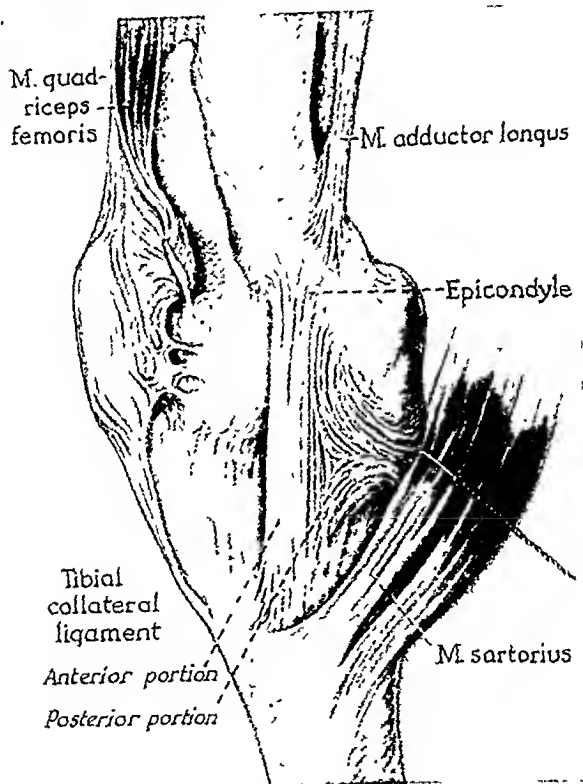


Fig. 2.—Drawing of lateral aspect of knee in extension, showing disposition of thick anterior portion of tibial collateral ligament and thinner posterior deltoid portion.

The posterior portion of the ligament is shorter and thinner than the anterior part. It is somewhat deltoid in outline, and its fibers radiate from the femoral and tibial origins of the main portion of the ligament to be inserted posteriorly on the medial fibrocartilage and the head of the tibia (Fig. 2).

Though the anterior and posterior portions are readily to be differentiated on their appearance alone, a more remarkable difference is noted on motion of the knee. The posterior portion of the ligaments becomes definitely taut in extension and markedly relaxed and redundant in flexion. *The anterior portion, on the contrary, remains taut*

*in all positions of the knee.* This is a noteworthy characteristic of the ligament, especially when consideration is given to the fact that the radius of curvature of the femoral condyle varies at different parts of its circumference. The fact that this portion of the ligament remains taut at all times is indicative both of the role it plays in maintaining the knee joint stability during all phases of its motion and of the necessity for restoring this tension in exactly the right plane if stability and unrestricted motion are to be obtained by any operative measure.\*

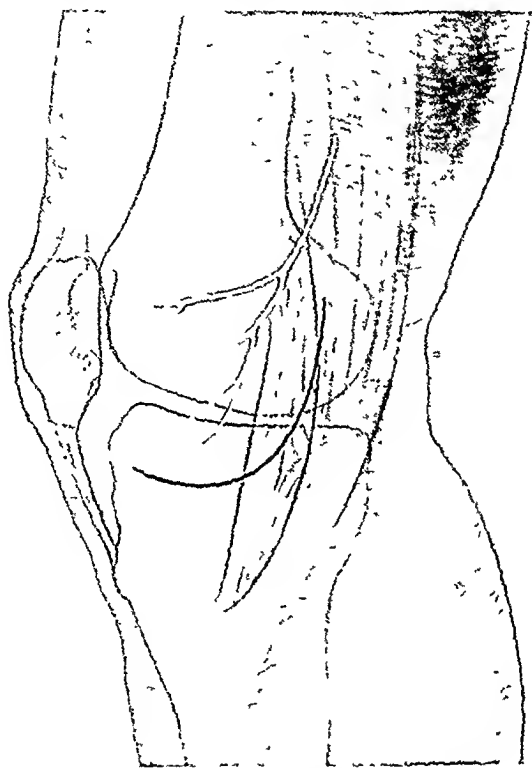


Fig. 3.—Transparent drawing showing relation of skin incision to bones and underlying soft tissues

In its present form the operation is relatively simple. A curved L-shaped incision, about 6 inches long, is made on the anteromedial aspect of the knee joint (Fig. 3). The vertical arm of the incision begins just below the level of the adductor tubercle and is carried downward to about 1 inch below the level of the articular surface of the medial tibial tuberosity. At this level the horizontal arm of the incision is carried anteriorly toward, but not quite to, the edge of the patellar ligament. (This incision runs roughly parallel to the infrapatellar branch of the internal saphenous nerve, injury to which is avoided.) The skin flaps are dissected back. The deep fascia and the quadriceps

\*Since the preparation of this paper, confirmation of these findings has appeared in a contribution by Brantigan and Voshell.<sup>2</sup>

expansion are incised in the same line as in the skin and reflected back as a separate layer. When this is finished, the tibial collateral ligament will be exposed in the posterior part of the incision. In the lower part of the wound, the anterior half of the medial meniscus will be seen extending from the anterior edge of the internal ligament forward to the patellar ligament. In this area the joint is opened and its medial half explored. The cartilage or crucial ligaments are treated, and the synovial membrane is again closed tightly.

The upper and lower attachments of the anterior portion of the tibial collateral ligament are now exposed and two drill holes are made at each end of the ligament by a  $\frac{3}{8}$  inch hand drill. The two upper drill holes are connected by a tunnel which passes transversely beneath the femoral attachment of the ligament, and the two lower drill holes are

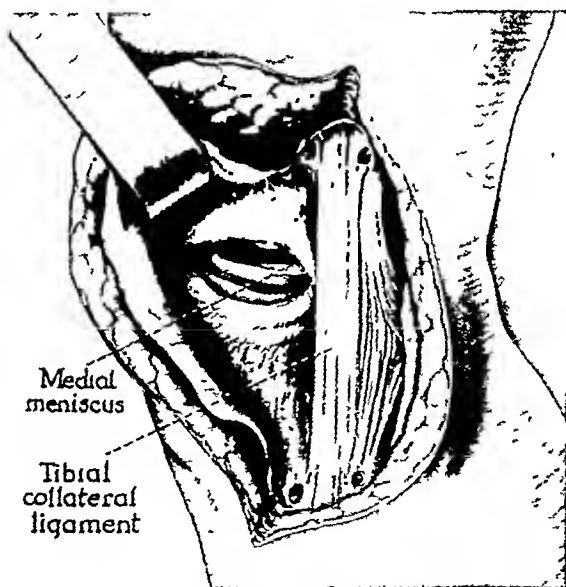


Fig. 4.—The joint is opened, exposing the semilunar cartilage. The drill holes in the bone for the fascial graft are shown.

similarly connected by a bone tunnel passing beneath the tibial attachment (Fig. 4). A piece of fascia 10 inches long and  $\frac{1}{2}$  inch wide is subcutaneously cut from the fascia lata of the same leg by means of a fascial stripper. The fascial graft is then passed in and out through the two upper drill holes, then down alongside of the tibial ligament, through the two lower drill holes, and back up to the origin. The leg is held in hyperadduction, and the remnants of the injured tibial ligament are sutured with several interrupted chromic stitches. This serves to maintain the leg in adduction on the femur and at the same time eliminates any tension on the graft during the period immediately following operation. The fascial graft is now sutured to the periosteum,

both at its entrance and exit, into the femoral drill holes. The graft is pulled down taut and again sutured at its entrance and exit from the tibial drill holes. The ascending limb of the graft is pulled taut and sutured to its free end. The medial collateral ligament is now outlined on four sides by a quadrilateral graft, the ascending and descending arms of which are visible, while the transverse arms are buried in the bone tunnels. The two vertical arms are next sutured to each other directly over the anterior part of the original collateral ligament so as to increase still further the tension under which they are placed (Fig. 5). The fascia and skin are then closed in layers with interrupted stitches, and a plaster of Paris bandage is applied, with the leg held in adduction. This is left on for a period of four to six weeks and is then removed and gentle active motion begun. Weight bearing may be begun at the end of six weeks, but as a matter of additional precaution, a knee cage brace should be supplied and the inner border of the shoe should be wedged to prevent excess tension on the new ligament.

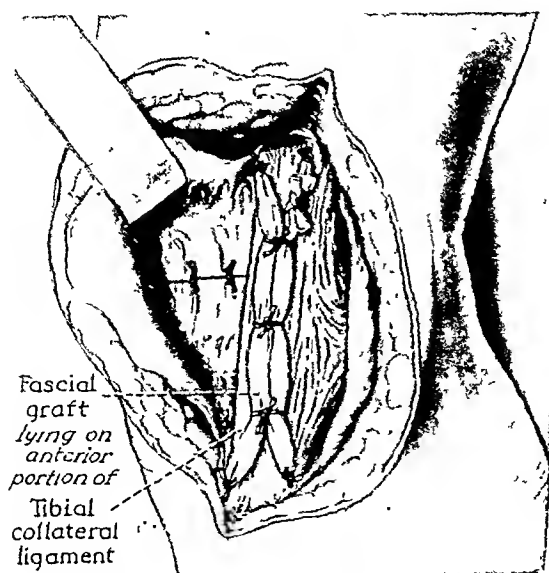


Fig. 5.—The joint is closed and the fascial suture is in place

In conjunction with other operations, the principle of this operation has been employed in about a dozen cases. By itself the procedure has been employed in 6 patients, 4 being cases of traumatic rupture, 1 being a case in which the ligament proved insufficient after an arthroplasty of the knee, and 1 being of congenital anomaly. All these cases were operated upon with the knee in extension, and in 5 there was satisfactory re-establishment of lateral stability in extension. In 1 case there was a slight lateral mobility, which in extension did not exceed several degrees but which in flexion appeared to be somewhat greater.

Despite this the patients were well pleased with the functional result and were able to resume their normal pursuits with but slight inconvenience. It may be that this slight defect could be overcome by making the fascial graft taut with the knee in flexion. This point should be further investigated. In the 1 case in which the result was considered unsatisfactory, infection occurred and the fascial graft sloughed out of the wound.

#### TRAUMATIC RUPTURE

##### *Satisfactory Results.—*

CASE 3.—B. G. was originally operated upon in February, 1934, after an injury to the left knee. At operation the anterior crucial ligament was found to be torn. The medial meniscus was fractured, and there was a marked laxity of the knee joint due to a *concomitant injury to the medial collateral ligament*. The cartilage was resected, and only the tibial collateral ligament was repaired in the manner previously described. The leg was encased in plaster for a period of six weeks, and thereafter gentle, active motion was begun. The patient was seen at intervals, the last being in January, 1938, at which time she had a completely stable knee, both in the anteroposterior and lateral planes, with normal, powerful extension of the knee joint and only the slightest degree of limitation of flexion. The patient complained of a slight sense of uncertainty in the knee, but she was able to engage in all of her usual activities without any limitation whatsoever.

CASE 4.—B. B., a markedly obese female, aged 45 years, was first seen in February, 1935, about one week after she had fallen down four steps, injuring her left knee. *She stated the knee had turned under her in hyperflexion and abduction* and after the accident she was unable to walk or bear weight upon the leg. The patient had to be taken home, and since then she had noted that whenever she attempted to stand upon her leg, the leg was unstable.

Examination disclosed moderate tenderness on pressure over the internal condyle and to a lesser extent over the external condyle of the tibia. Anteroposterior and lateral hypermobility were present. The left knee could only be flexed to about 15° beyond a right angle, at which point the patient complained of pain. X-ray of the left knee was reported as being radiographically negative. Operation was advised and performed on Feb. 28, 1935. At operation the medial half of the postpatellar fat pad was found to be contused. The posterior half of the internal semilunar cartilage was fractured. Both crucial ligaments were torn, the anterior at its mid-portion and the posterior slightly below its femoral insertion. The deep fibers of the internal lateral ligament were torn at their tibial attachment, and the ligament was definitely relaxed. The anterior crucial ligament was resected along with the internal semilunar cartilage. The posterior crucial ligament was sutured with chromic catgut. The internal lateral ligament was sutured and then reconstructed by a fascial graft in the manner described above. Complete immobilization of the knee by means of plaster was extremely difficult because of the patient's obesity. Nevertheless, fairly efficient adduction of the knee was maintained for a period of about six weeks, after which time the plaster was removed and exercises were commenced. The patient made an uneventful recovery with restoration of stability and functional capacity of the knee.

CASE 5.—G. G., male, 14 years of age, was first seen in the hospital on May 4, 1936. He stated that two and one-half years before he had been in an automobile accident in which he had suffered a fracture of the skull and contusion of the left knee. About one year later, while broad jumping, his knee gave way under him and

he fell. Although no swelling of the knee was noted at the time, the patient complained of a dull pain on the inner aspect of the left knee. He has had two other attacks of giving way of the knee, but there was no history of locking or clicking. The last attack occurred about three months before the examination.

Examination disclosed only slight tenderness over the internal collateral ligament and a marked degree of both anteroposterior and lateral hypermobility. On forcible abduction of the leg, a gap of about  $\frac{3}{4}$  inch could be opened up between the tibial and the femoral condyles. X-ray showed a chip fracture on the inner aspect of the left tibia immediately below the proximal epiphyseal line. A diagnosis of a torn tibial collateral ligament was made, and operation was advised and performed on May 7, 1936.

At operation both crucial ligaments were found to be completely torn and were represented only by small stumps, which could not be sutured. The internal semilunar cartilage was removed, and a fascial plastic on the tibial collateral ligament was performed. Immediately after completion of the operation all anteroposterior mobility disappeared, leaving only a very slight amount of lateral mobility, which was corrected by reefing the medial half of the patellar retinaculum. After the usual period of immobilization in a plaster of Paris bandage, motion was started and gradually increased.

At examination on May 11, 1939, a matter of three years after operation, the patient had a completely normal range of flexion and extension. In extension there was the very slightest trace of lateral mobility noted, not exceeding 2 or 3°. Anteroposterior mobility was completely absent. The patient stated he was able to engage in all of his normal activities, although he occasionally complained of a slight sense of weakness in the knee.

### *Unsatisfactory Result.—*

CASE 6.—E. D., male, aged 30 years, was seen in January, 1939, following an injury about five weeks before in which he had slipped on a pile of old iron and twisted his left knee. Despite severe pain the patient continued at his work for that day, but on the following day he was unable to work because of swelling and inability to bend his knee. Under rest and hot applications the swelling disappeared, but the patient noted intermittent episodes of locking, clicking, and giving way of the knee. On crossing his knees he noted occasional clicking sensation in the joint.

Examination disclosed no fluid in the knee joint and no crepitus on motion. Powerful, active extension to 165° was possible. Passively, the knee could be extended to 180°. Flexion was normal. There appeared to be some tenderness over the anterior horn of the internal semilunar cartilage, with accentuation of the tenderness on extension of the leg. With the knee in extension about 15° of hyperabduction was possible and the joint could be opened sufficiently to see the outlines of both the femoral and tibial condyles beneath the skin along the inner aspect. In the flexed position there was a slight increase in anteroposterior mobility. There was marked tenderness over the tibial attachment of the tibial collateral ligament.

The x-ray showed a slight shadow in the region of the crucial spine but was otherwise negative. The patient was considered to be suffering from a tearing of the tibial collateral ligament, and operation was advised.

At operation, which was performed on Jan. 26, 1939, the tibial collateral ligament was found to be torn almost completely across at the level of the upper surface of the medial meniscus. It is to be noted, however, that this did not correspond with the area of tibial tenderness. Upon opening the knee joint, the medial meniscus was found to be torn across at its posterior portion. The crucial ligaments were apparently intact. A fascial plastic reconstruction was performed and after closure of the wound, a plaster of Paris bandage was applied, immobilizing the knee.

The patient developed a slight temperature, and on examination of the wound a low-grade infection was found. This persisted for several weeks with a necrosis of a considerable portion of the fascial graft. At the end of six weeks the plaster was removed and a knee-cape brace was supplied to the patient.

Examination in August, 1939, disclosed slight, but quite definite, lateral instability with the knee in extension. Flexion was limited at  $110^{\circ}$  and active extension was possible to  $175^{\circ}$ . The patient stated that though there was a marked improvement as compared with the condition before operation, he did not have the sense of complete security which had been expected. This case was considered extremely valuable. Though the result could at best be considered mediocre, it definitely established the fact that (1) the tibial reconstruction obviated the instability and (2) secondary infection, with necrosis of the fascial graft, resulted in partial recurrence of the instability.

#### INSTABILITY FOLLOWING ARTHROPLASTY

##### *Satisfactory Result.*—

CASE 7.—J. LaF., female, aged 23 years, was first seen in the hospital in March, 1937, four and one-half years after an abortion, as a result of which the patient developed a septic infection of the right knee. The patient was under treatment for this infection for a period of about one year, after which time she was discharged from treatment with bony ankylosis of the knee in the position of flexion. For three years prior to her admission to the hospital she had had no signs of any acute inflammatory process and she applied for treatment for correction of the ankylosis.

Examination disclosed the knee fixed at an angle of  $130^{\circ}$ , and the x-ray showed this was due to bony ankylosis. On April 29, 1937, an arthroplasty of the knee was performed with excellent result. When examined in July, 1938, it was noted, however, that though the patient could flex the knee to  $90^{\circ}$  and extend it to  $180^{\circ}$ , there was marked lateral instability. The knee could be abducted to a distance of 10 to  $15^{\circ}$ , and the patient complained of a sense of insecurity. On July 21, 1938, a fascial reconstruction of the tibial collateral ligament was performed, and the leg was immobilized in plaster. After seven and one-half weeks the plaster was removed and motion begun. In September, 1938, it was noted that there was absolutely no lateral instability in the extended position and flexion was possible to  $140^{\circ}$ .

In November it was noted that the range of flexion had not been increased, and x-ray disclosed that this was due to a bony excrescence on the tibial surface, which was a consequence of the arthroplasty and had caused no interference with motion until the normal tension of the ligamentous apparatus had been restored by the operative reconstruction of the tibial collateral ligament. Despite this limitation of flexion, the patient expressed herself as being definitely satisfied with the result of the operation, since the pain in the knee previously noted had disappeared and she was able to walk about with stability. The advisability of a reoperation for the removal of the articular excrescence is still under consideration.

This case is of particular importance in justifying the procedure here suggested, since it is to be presumed that following the infection and the arthroplastic procedure, the tibial collateral ligament must have been largely destroyed. In cases such as this the necessity for reconstruction of a new ligament is, of course, beyond question.

#### MULTIPLE CONGENITAL DEFORMITIES WITH RELAXATION OF TIBIAL COLLATERAL LIGAMENT

CASE 8.—R. H., female baby, aged 2 days, was brought to the Out-Patient Department on Feb. 3, 1933. The patient, the last of three children, was a breech

presentation and was delivered without instrumentation by podalic version. Immediately after birth marked bilateral clubfoot, right genu valgum, and left genu varum were observed (Fig. 6). Examination disclosed that in addition the child was suffering from a congenital dislocation of the left hip and congenital dislocation of the right patella.

Numerous procedures, both open and closed, were undertaken for the correction of the clubfeet and for the hip dislocation. Since they are not of primary interest to the present discussion, the details of these treatments may be omitted.

The right knee presented an interesting combination of bony and ligamentous anomalies. The leg could be abducted on the femur to about  $35^{\circ}$  from the normal position to which it could be passively brought back. Extension at the knee was possible to  $180^{\circ}$  and flexion was limited at  $150^{\circ}$ . The patella, obviously maldeveloped, was laterally displaced above the external femoral condyle and was clearly riding high above the normal level. In addition, the roentgenogram disclosed a flattening of the distal femoral epiphysis and a typical tibia valga.



Fig. 6.—Photograph on admission showing deformities of feet and legs.

It was apparent that this knee was the locus of a number of different conditions, each of which required essentially different treatment. In the effort to correct the underlying bony abnormality, a plaster of Paris bandage was applied in 1934 and was gradually wedged to correct the tibia valga. Unfortunately, this had to be discontinued because of an inadvertent fracture of the lower end of the femur, which ultimately healed in fairly satisfactory position.

In 1936 the patient was admitted for osteotomy of the tibia. In 1938 the patient was admitted for treatment of the patellar dislocation and the limitation of knee flexion. The quadriceps tendon was lengthened by a Z-shaped incision. The knee was then completely flexed and numerous adhesions, both peri- and intra-articular, were disrupted. An elliptical flap of capsule was then removed from the inner aspect and transferred to the outer aspect of the knee joint capsule. The outer



long tongue of the Z-shaped tenotomy was then sutured to the inner long tongue and the wound closed. The knee was bandaged in flexion. Despite the routine slough of the overlying skin, the wound finally healed, and both active and passive motion was instituted. Ultimately, the patient was able actively to extend the knee to about  $170^\circ$  and to flex it to about  $90^\circ$ .

In the early part of 1940 the patient was again admitted to the hospital for the correction of the lateral hypermobility which still was possible to  $30^\circ$  from the midposition. The operation above described was performed on March 12, 1940, as a completely extra-articular procedure, since there was no need for exploration of the joint. On the operating table it was noted that immediately after reconstruction of the tibial collateral ligament, the lateral hypermobility was completely overcome, and the leg was held in a slightly bowlegged position. However, it was noted that passive flexion was limited at about  $130^\circ$ . The leg was immobilized in the usual manner and for the usual time. Following this, physiotherapy was instituted. In October, 1940, the range of flexion had increased to  $115^\circ$ , and this has since still further improved so that flexion is possible almost to a right angle. With the leg in flexion a few degrees of lateral mobility still exists, but in extension the stability of the knee is excellent. A slight genu valgum has recurred, but this is due to a flattening of the distal femoral epiphysis and will probably necessitate a later supracondylar osteotomy.

#### SUMMARY

The surgical reconstruction of the tibial collateral ligament here presented has been employed since 1934. The satisfactory results from its successful restoration and the unsatisfactory result of the failure confirm the significance of the tibial collateral ligament in the function of the knee.

The procedure is completely extra-articular, though the approach is such as to permit ready access to the joint for exploration if deemed necessary. It is applicable to all relaxations of the tibial collateral ligament, regardless of the point at which rupture occurs. Since this ligament may tear at any portion of its continuity from the femoral origin to the tibial insertion, the method seems to possess special merit, particularly in those cases in which the site of rupture cannot be predetermined with accuracy. It is based on an anatomical conception of the tibial collateral which is different from that commonly accepted. It demonstrates that the only necessary element in the reconstruction is the accurate placing of the graft directly over the course of the anterior portion of the tibial collateral ligament.

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# A NEW CLAMP FOR ASEPTIC ANASTOMOSIS IN GASTROINTESTINAL SURGERY

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THAT aseptic anastomosis in gastrointestinal surgery has long been considered a desideratum is readily evinced by the voluminous literature which has been amassed on this subject and the numerous ingenious instruments that have been devised for this purpose. However, in spite of these perennial contributions and reiterations of the obvious advantages of this method, the open anastomosis remains yet the most commonly employed procedure. It becomes obvious, therefore, that a satisfactory method of aseptic anastomosis has not been evolved. This has been due in great measure to certain objectionable features inherently present in practically all instruments utilized for this purpose. The instrument here to be described is presented with the belief that these difficulties and objections are obviated and the procedure can be performed with greater facility and simplicity.

The instrument consists of a strong crushing clamp similar in construction to the Rankin clamp<sup>2</sup> except for the absence of the middle blade (Fig. 1), two thin-bladed clamps, and a clamp holder (Fig. 2). The thin-bladed clamps consist of long, slender, narrow blades to permit the "turning in" of a minimum amount of bowel wall and have longitudinally grooved opposing surfaces to allow a firm grip. The open ends of the blades are so threaded that when the blades are approximated, a nut may be screwed on, thus locking the clamp in the closed position. To the hinged end of the blades is attached a pin which may be inserted into corresponding holes in both the crushing clamp and the clamp holder for securing the blades in the correct positions. The clamp holder consists of a handle with two parallel round holes at one end into which the pins of the thin-bladed clamp are fitted and secured.

The instrument may be used to perform aseptically various types of anastomoses, such as end-to-end, side-to-side, or end-to-side, following gastric or intestinal resections, as well as the closure of a blind end of bowel. However, for purposes of expediency, only one type, an end-to-end anastomosis, will be described.

The thin-bladed clamp is fitted into the large crushing clamp, secured in place by tightening the wing nut, and the blades opened widely (Fig. 3). The bowel, which previously has been appropriately prepared for resection, is placed between the blades at the desired site of division and crushed (Fig. 4a). The nut is screwed on the ends of the thin-bladed clamp and the crushing clamp opened and removed, leaving the crushed

bowel wall firmly held within the slender blades of the thin-bladed clamp (Fig. 4b). Thus, it may be readily observed that the purpose of the heavy crushing clamp with the thick strong blades is to transmit the crushing force which could not be obtained by the thin slender blades. However, once the bowel wall is crushed, the thin blades are sufficiently strong to hold securely the coapted surfaces. An Ochsner or Payr clamp is applied immediately adjacent to the thin-bladed clamp and the bowel divided between them with the cantery (Fig. 5a). This procedure is repeated at the other end of the intended site of division and the resected

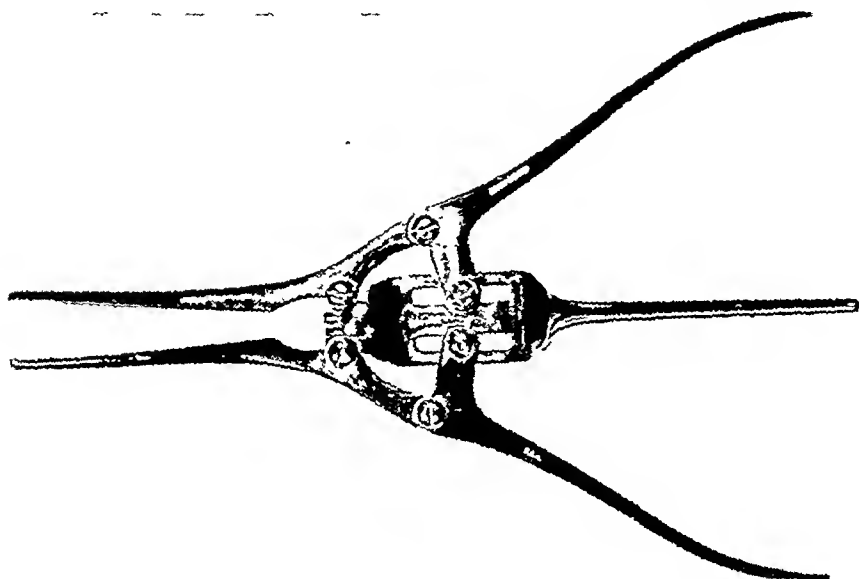


Fig. 1.—Photograph of the strong crushing clamp.

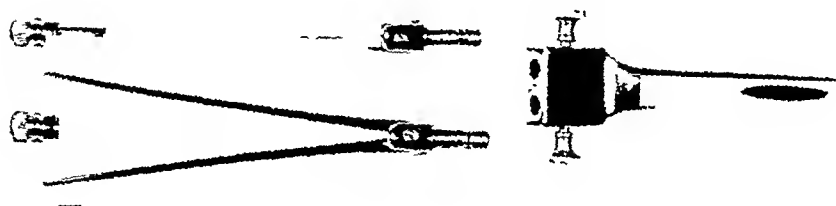


Fig. 2.—Photograph of thin-bladed clamps and clamp holder.

bowel included between the Ochsner and Payr clamps removed. Thus, it is observed that the large crushing clamp remains sterile because it is always removed before the bowel is divided. In this way only one large crushing clamp is necessary, although several thin-bladed clamps may be utilized in the operation. The thin-bladed clamps containing the proximal and distal ends of the bowel are then placed in the clamp holder by inserting the pins at the hinged ends into their respective holes in the clamp holder. The blades are then rotated, one clockwise and the other

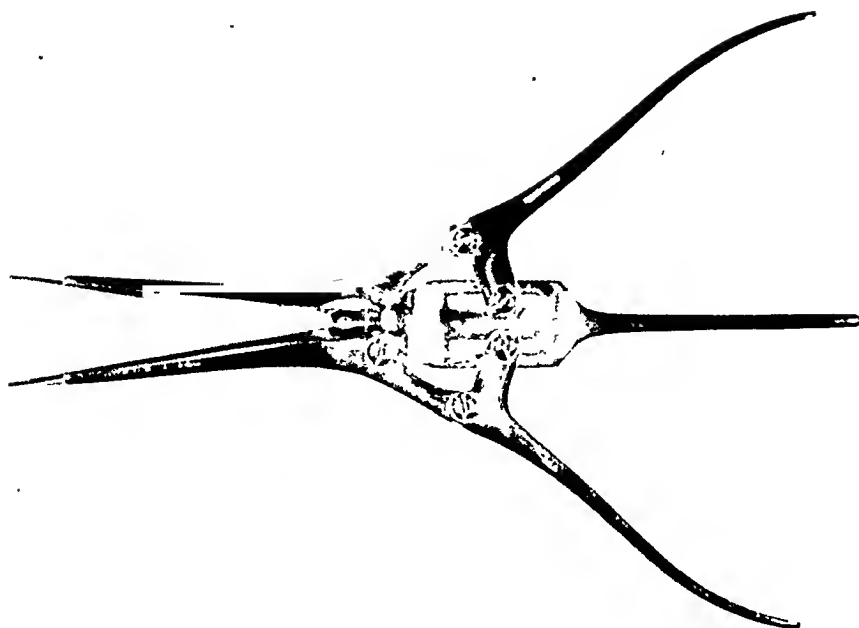


Fig. 3.—Photograph of crushing clamp with thin-bladed clamp secured in place.

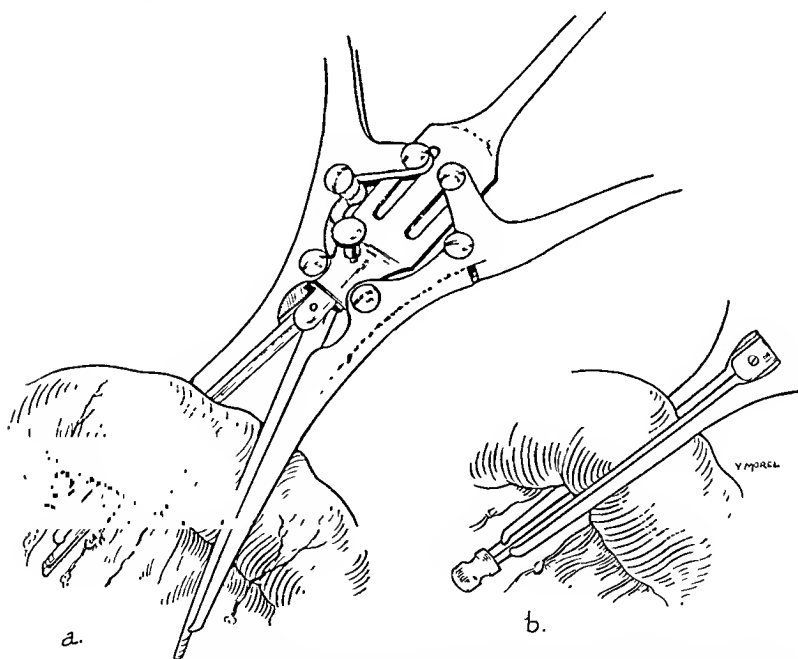


Fig. 4.—Drawing showing use of clamp in end-to-end anastomosis following resection of segment of bowel: (a) The bowel, which previously has been appropriately prepared for resection, is placed between the blades at the desired site and crushed. (b) The nut is screwed on the ends of the thin-bladed clamp and the crushing clamp opened and removed.

counterclockwise, in their longitudinal axis, so that the posterior wall of the respective ends of the bowel approximate each other more closely during the installation of the posterior row of sutures (Fig. 5b). The clamps are held firmly in this position by tightening the wing nuts against the pins in the clamp holder. Attention is directed to the necessity of placing the bowel at the intended sites of division in symmetrical portions of each clamp. This is considerably facilitated by the fact that the thin-bladed clamps are graduated in centimeters. In this way

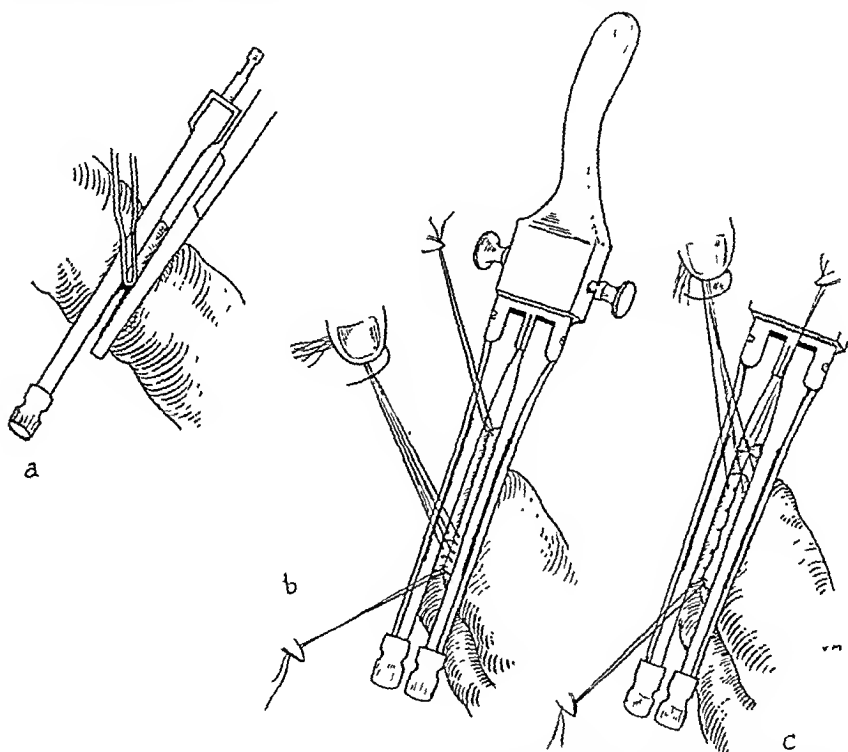


Fig. 5.—(a) An Ochsner clamp is applied immediately adjacent to the thin-bladed clamp and the bowel divided between them with the cautery. (b) After repeating the procedure illustrated in Figs. 4 and 5a, the thin-bladed clamps containing the proximal and distal ends of the bowel are placed in the clamp holder by inserting the pins at the hinged ends into their respective holes in the clamp holder and rotated and adjusted so that the posterior wall of the respective ends of the bowel approximate each other. The clamps are held firmly in this position by tightening the wing nuts against the pins in the clamp holder. The first posterior row of sutures is installed by using interrupted Cushing stitches of quilting cotton. (c) These sutures have been tied and severed, and a second row is similarly installed nearer the edges of the blades.

the proximal and distal ends of the bowel lie exactly opposite each other when the clamps are placed in the clamp holder. However, some adjustment can be made by inserting the pins of each clamp to the desired depth for accurate approximation of the respective ends of the bowel. The first posterior row of sutures is installed by using interrupted Cushing stitches of quilting cotton<sup>1</sup> (Fig. 5b). These sutures are tightened, tied, and severed and a second posterior row similarly installed nearer the edges of the blades (Fig. 5c).

The wing nuts are loosened, permitting rotation of the clamps toward each other, and the second posterior row of sutures tied and severed. The clamps are rotated a little more toward each other and the wing nuts of the holder tightened. The first anterior row of sutures is installed, using interrupted Cushing stitches of quilting cotton (Fig. 6a). The lock nut on the end of each clamp is unscrewed, permitting the blades to open, and as the clamps are removed, the sutures are tightened, thus approximating the bowel edges (Fig. 6b). After these sutures are tied and severed, the second anterior row is similarly installed and additional sutures are placed at the ends through which the blades projected, thus completing the anastomosis except for closing the rent in the mesentery (Fig. 6c). The crushed ends are opened by manipulation between the thumb and forefinger of the anastomosis through the bowel wall (Fig. 6d).

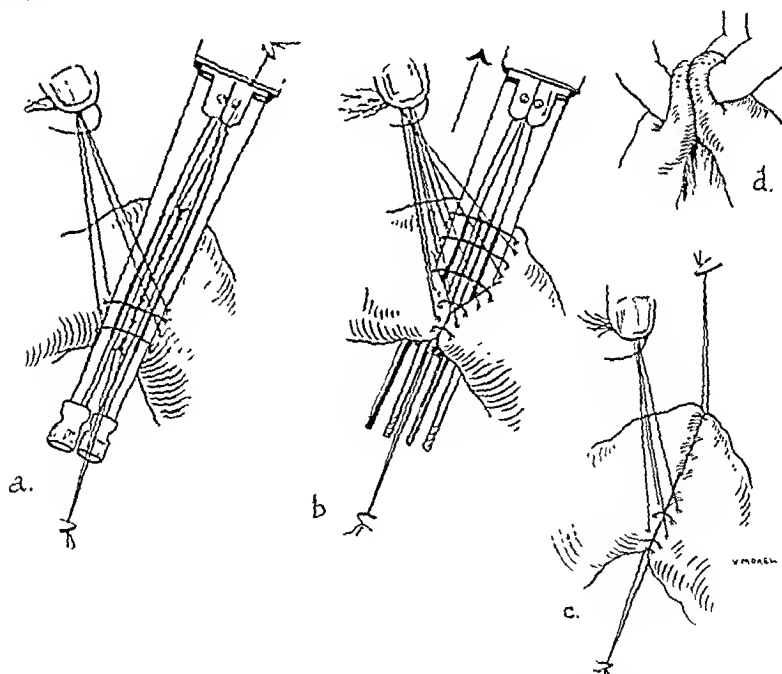


Fig. 6.—(a) The wing nuts have been loosened, permitting rotation of the clamps toward each other, and the first anterior row of sutures is installed, using interrupted Cushing stitches of quilting cotton. (b) The lock nut on the end of each clamp is unscrewed, permitting the blades to open, and as the clamps are removed, the sutures are tightened, thus approximating the bowel edges. (c) The sutures of the first anterior row have been tied and severed, and a second row is similarly installed and additional sutures placed at the ends and in the rent in the mesentery, thus completing the anastomosis. (d) The crushed ends are opened by manipulation between the thumb and forefinger of the anastomosis through the bowel wall.

The instrument was first tried on fresh autopsy specimens and its efficacy demonstrated. It was then used on the Tulane Surgical Service for the performance of various types of anastomoses. The simplicity and facility of performing aseptic anastomoses with this instrument in gastrointestinal surgery have been definitely established. The signifi-

cance of aseptic gastric resection has been recently emphasized by Wangensteen<sup>3</sup> and this instrument is readily adaptable to this procedure, although another size clamp having longer blades is necessary.

The obvious advantages of this instrument\* are numerous. It permits a safe, simple, effective, and easily performed aseptic anastomosis. Because of the thin, slender blades of the clamp, a very small amount of bowel wall is turned in. The installation of the anastomotic sutures is considerably facilitated by the stable manner in which the bowel is maintained by the clamp holder, thus minimizing trauma of manipulation and obviating the necessity of other hands in the field. Moreover, because the posterior rows of anastomotic sutures can be placed just as readily as the anterior from the same position, turning the bowel ends over is unnecessary. This is a real advantage in certain types of anastomoses because of the awkwardness and difficulty which may be encountered in completing the posterior rows of sutures. Since only one large crushing clamp is necessary, the original cost and maintenance of the instrument are kept at a minimum.

#### REFERENCES

1. Ochsner, Alton, and Meade, William H.: Spool Cotton As a Suture Material, J. A. M. A. 113: 2230-2231, 1939.
2. Rankin, F. W.: An Aseptic Method of Intestinal Anastomosis, Surg., Gynec. and Obst. 47: 78, 1928.
3. Wangensteen, Owen H.: Aseptic Gastric Resection, Surg., Gynec. and Obst. 70: 59, 1940.

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\*The instrument has been manufactured through the courtesy of A. S. Aloe and Co., St. Louis, Mo.

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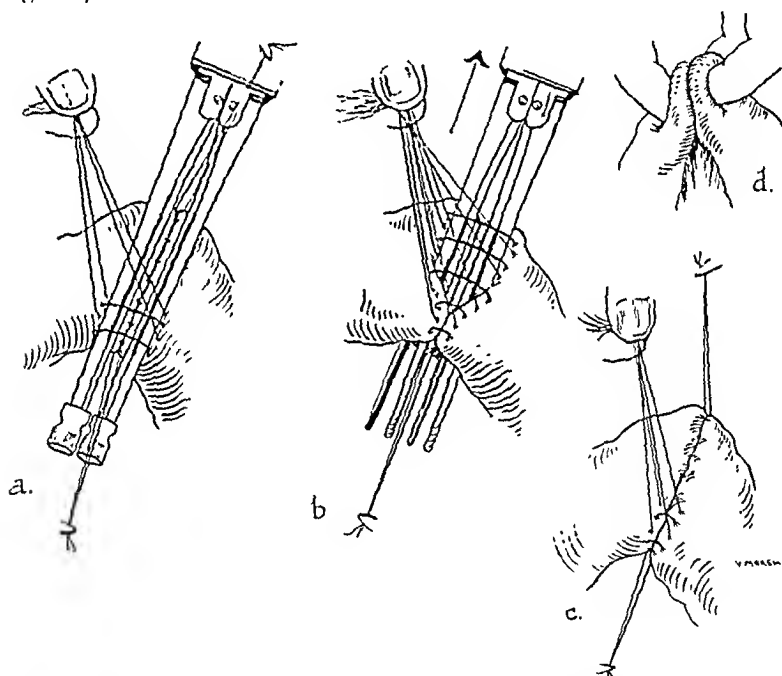


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## AN IMPROVED COLOSTOMY OUTFIT

GEORGE F. ARCHER, M.D., AND JULIAN G. RILEY, M.D.,  
ATLANTA, GA.

A PERMANENT colostomy is an unfortunate handicap; about this there can be no argument. But it very definitely is not the intolerable thing that it has been considered in the past. With the proper management it is possible for a patient with a permanent colostomy to lead an approximately normal life.

The successful management of a colostomy depends on several things. First, the exact nature of the colostomy, its location, how much prolapse is present, and the direction in which its opening points. It is much easier for a patient to keep himself clean if his colostomy points downward and medially. Second, the intelligence and cleanliness which the patient displays in the care of his colostomy. And third, the type of colostomy outfit which he employs.

Ideally a colostomy should be so trained that it performs its function only at a given time each day. Since this, for practical purposes, is impossible, a colostomy bag or pouch is at present a necessary evil. The outfit employed should be of such a nature that it can be worn comfortably, that it requires little attention from the patient, and that it can be kept so clean that it is not surrounded by the disagreeable odor which all too frequently envelopes colostomy patients.

Many colostomy outfits have been devised but none of these has proved entirely satisfactory. The one about to be described was designed by a patient, Mr. C. D. Graves. It more nearly approaches an entirely satisfactory colostomy outfit than any other we have had occasion to see. For this reason we feel that it should be brought to the attention of the medical profession.

Fifteen years ago, following a two-stage operation performed by William Mayo for carcinoma of the rectum, Mr. Graves was left with a permanent colostomy. A colostomy bag was recommended for his use but did not function satisfactorily enough to permit the mingling with other people required by Mr. Graves' profession. Several other types of colostomy bags were investigated but seemed to offer no advantage over the one he had been wearing. Mr. Graves, being an intelligent and resourceful man, then began to experiment on himself with various homemade colostomy outfits. After fourteen years of self-experimentation he has gradually developed his present colostomy bag-tank which he now wears and feels to be highly satisfactory.

Mr. Graves' colostomy outfit is composed of the following parts:

1. A washer, worn against the abdominal wall; this is a wax-coated, thin, flat, rubber washer with a flared inner edge. One rim of the washer is cut, allowing the ends to be overlapped, stitched together, and made to fit snugly around the individual colostomy. Extra washers of varied sizes are available.

2. The colostomy tank; this is made of wax-coated rubber stretched over a metal rim. A hole about one and one-half inches in diameter placed near one edge of the tank receives the colostomy stoma.

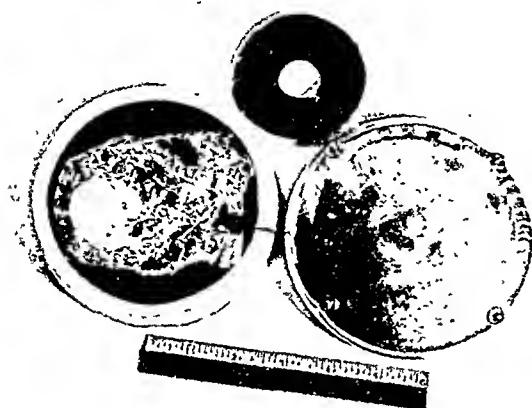


Fig. 1.

Fig. 1.—The unassembled colostomy outfit; rubber washer, cellophane bag, colostomy tank, and aluminum front.

Fig. 2.—Shows how the neck of the bag is drawn through the back of the tank and how the aluminum front fits in place.



Fig. 2.

3. Cellophane bags one-half or one pound size; these may be procured from any ten-cent store. The mouth of the paper bag protrudes through the hole in the back of the tank and is held snugly between the tank and the rubber washer.

4. The aluminum front of the tank; this fits snugly into the tank and the entire outfit is held in place by two elastic belts that snap onto the tank front. The tank front can be obtained in either of two sizes. The thinner of these has a depth of slightly less than one inch and can be worn when inconspicuousness is essential.

The wax used to coat the washers and the tank (except the aluminum front) is gulf wax. It can be bought at any ten-cent or grocery store. Its melting point is such that at body temperature it is soft enough to form a snug pliable junction. It permits the parts of the colostomy outfit to be cleaned and does not retain a fecal odor. Each time the bowels move, the cellophane bag is discarded, the washer rinsed with water and dried, and a new bag inserted in the tank.

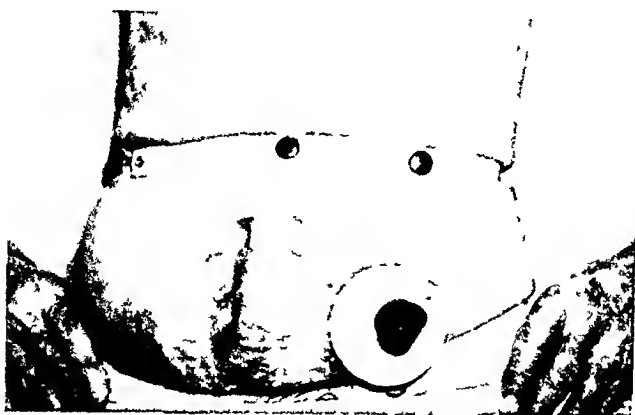


Fig 3—First stage in putting on the colostomy outfit. The belts are in place and the washer has been slipped over the colostomy stoma

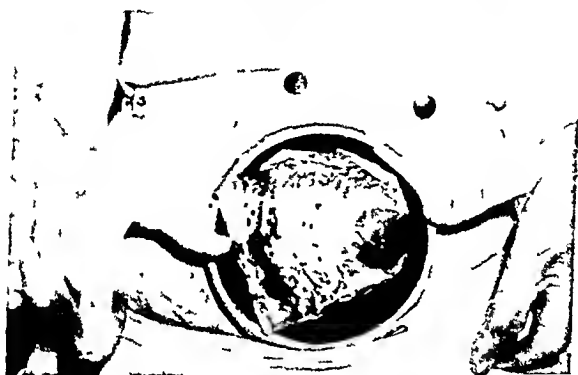


Fig 4—Second stage. The tank proper with its reservoir bag has been placed over the colostomy stoma and lies against the washer and the abdominal wall

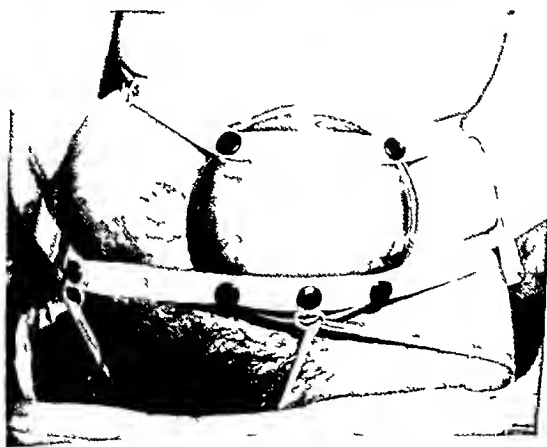


Fig 5—Third stage. The aluminum front has been applied to the tank and the entire outfit is held in place by two elastic belts

Several advantages of this colostomy outfit are immediately apparent. Most important, the paper bags in which the fecal material is collected are easily and inexpensively obtained from any ten-cent store. They can, with a minimum contamination of the fingers, be removed, discarded in a water closet, and replaced. It is possible for the wearer to continue at his work even with a severe diarrhea. The use of two paper bags, one within the other, is said to keep at a minimum the odor from escaping colostomy gas. Wax-coated rubber is more easily cleaned than rubber not so coated and will not retain the odor of feces. A new coating of wax is easily applied by immersing, for a moment, the washer and tank in melted wax. Should the wearer of a bag-tank be caught in an afternoon subway rush, he need have no fear that a jostling crowd might cause him to soil himself. The tank protects him against blows and the belts hold it securely in place.\*

During fifteen years of colostomy life, Mr. Graves has developed several little tricks which make easier the management of his colostomy. While taking a bath, he effectively closes his colostomy by tying it loosely with a single overhand knot of cotton rope. The piece of rope used is eight to nine inches long and is made by rolling between the hands B. & B. cotton, cut one-half inch wide with the fiber. Such a piece of cotton rope has enough tensile strength to close the colostomy but will not injure the bowel wall. It can be used again and again. In cleaning a soiled colostomy, it is important that the material used shall not be irritating to the mucous membrane. Wet kleenex or a wet soft toilet tissue, such as scot tissue, serves very well for this purpose.

We do not claim that this colostomy outfit is any panacea for all the troubles of a colostomy patient. There will be times when any such patient will soil himself in spite of all that he can do. However, we do feel that Mr. Graves' colostomy outfit represents a definite advance in the successful care of a permanent colostomy.

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\*Made by Mr. C. D. Graves, Dublin, Ga.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT PROGRESS IN THE SURGICAL TREATMENT OF LUNG TUMORS

W. E. ADAMS, M.D., CHICAGO, ILL.

(From the Department of Surgery of the University of Chicago)

CURATIVE surgical treatment of primary lung tumors has been one of the most recent accomplishments in the field of thoracic surgery. Although rapid progress has been made by this specialty since World War I of 1914 to 1918 little success attended the treatment of lung tumors until within the past decade. As noted by Churchill<sup>1</sup> in 1933, articles and monographs dealt with all aspects of the subject except treatment which was "either not mentioned at all, or dismissed as was the March Hare's wine—"There isn't any." This view was substantiated by Carlson and Ballou<sup>2</sup> (1933), who in an exhaustive review of the literature were able to find only one patient surviving five years,<sup>3</sup> and another three years after resection (lobectomy). All others expired within two years or less of metastases or of local recurrence.

Thoracic surgery in general has lagged far behind abdominal surgery in its development, although Gluck<sup>4</sup> stated that surgery of the lung followed the rule of general surgery: "*Ubi haemorrhagia ibi ligatura, ubi tumor ibi extirpatio, ubi pus ibi incisio.*" Réclus,<sup>5</sup> in an address at the French Surgical Congress in 1895, disagreed with Gluck, stating that "the structure of the lung and its air passages, the part it plays in sustaining the life of the blood, its relations with the heart and the presence of a pleural cavity all forbid great expectations and limit the power of the surgeon. Resection of a part of the lung for primary malignant disease is not even worth discussing. An accessible, single circumscribed growth would be a clinical wonder that would evade our present powers of observation." Subsequent events have substantiated Gluck's, rather than Réclus', point of view, when certain principles particularly applicable to the thorax are observed. That success was not forthcoming in the case of lung tumors until within recent years is difficult to understand.

S. Paget,<sup>6</sup> one of the foremost men in this field of his time, published the first comprehensive work on thoracic surgery in 1896. His book was occupied chiefly with traumatic wounds of the chest, infections and tumors of the chest wall, and empyema. Of the 462 pages,

less than 10 were devoted to intrathoracic malignant tumors and these were concerned chiefly with case reports. His prediction for the future could not have been farther from the truth when he stated: "It is sometimes said that surgeons fifty years hence will think as little of our results as we think of the methods of fifty years ago. So far as regards the surgery of the chest, this is utterly untrue. Fifty years ago it had risen above the horizon. It is now nearly at its zenith."

A careful survey of the factors involved which have delayed the successful surgical management of lung tumors enables one to group them under three headings: (1) altered cardiorespiratory function due to disturbance of intrathoracic pressures, (2) methods of diagnosis, and (3) resection of pulmonary tissue.

#### PHYSIOLOGIC CONSIDERATIONS

One of the major factors which retarded intrathoracic surgery was the fear of an open pneumothorax. The dangers associated with this condition were recognized by the ancient Greeks, but they understood little of the underlying principles on which this was based. As early as the sixteenth century, however, some knowledge of the influence of altered intrathoracic pressures on cardiorespiratory function was gained from animal experimentation.

The anatomist at Padua, Vesalius,<sup>7</sup> demonstrated the dangers of an open pneumothorax to his students. He exposed the transparent parietal pleura, through which the movements of the lung could be seen. On breaking this membrane the lung would fall away from the side wall, but the motion of the chest remained unchanged. If the other pleural cavity was opened, "the lungs are seen as the result of perforation to fall together and collapse. The cardiac motion may not be observed for long, since suffocation of the animal will come on account of the collapse of the lungs. In order to restore the life of the animal, an opening is made in the upper part of the trachea, into which a pipe made from a reed is introduced and when it is broken into, if the lung rises up, the animal receives air. The lung should be inflated to the degree to which it occupied the thorax in life. The heart now gathers strength and its motion will change beautifully. Therefore, by maintaining repeated inflation of the lung, you may have opportunity to examine the motion of the heart both by touch and sight as much as you desire."

Thus we see that Vesalius understood both the untoward effects upon the cardiorespiratory function of open pneumothorax with its alterations of intrathoracic pressures, and a means of avoiding these deleterious effects or of overcoming them once they were established. For centuries, the dangers of an open pneumothorax were remembered, but the principle involved in the method of overcoming or obviating them was forgotten, or at least it was not associated with thoracic problems.

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Duval's opinion is found in the use of spinal anesthesia for a considerable number of thoracotomies, notably in Canada and in England, without serious deleterious effects. As stated by Edwards,<sup>16</sup> "when the chest is widely opened and the lung is free from adhesions and collapsed, a patient under spinal anesthesia, i.e., at complete rest, is able to breathe comfortably and easily. If, however, cough occurs, there is invariably some respiratory distress which, if minimal, will settle in a moment or two, but if more severe, can only be controlled by the administration of a little oxygen given under slight positive pressure with a firm-fitting face piece." Why there exists the discrepancy between different patients under similar circumstances is not entirely clear. However, one fact is definitely understood; namely, coughing is not well tolerated during the presence of open pneumothorax without some

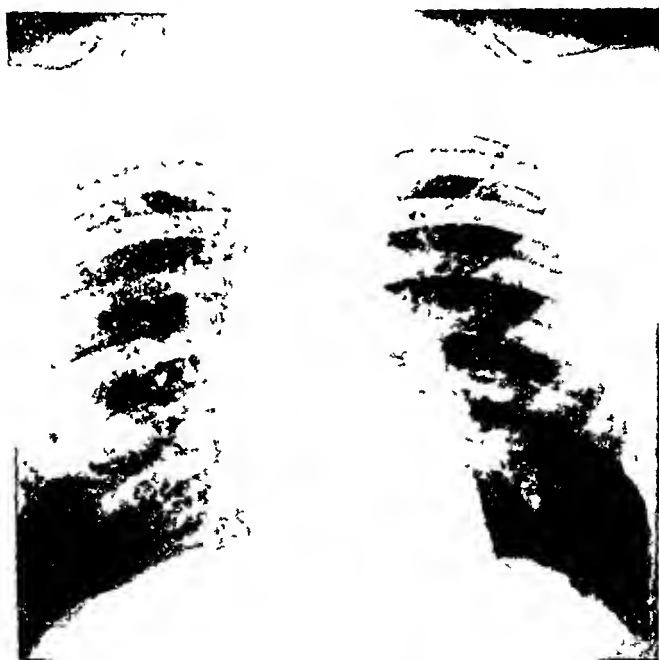


Fig 2—X-ray of chest of a 56-year-old male with a squamous-cell carcinoma of the left primary bronchus. The increased hilar shadow is characteristic of the lesion in this location with beginning bronchial obstruction, pneumonitis, and atelectasis.

elevation of the pressure within the tracheobronchial tree. Whether this is on the basis of side-to-side movement of the mediastinum with its deleterious effects upon the normal insufflation of the opposite lung, or whether it interferes materially with the return flow of blood to the heart and consequently diminution of the cardiac output is not definitely understood. However, both of these functions are probably altered. It is well known that a correction of these deleterious effects, aggravated by coughing, can be quickly and easily brought about by the administration of oxygen under a low positive pressure.

Methods, procedures, and even principles seem to have a way of being reborn or discovered again and again and so it was with the present principle involved. Von Mikulicz<sup>8</sup> set Sauerbruch<sup>9</sup> to work upon the problem of intrathoracic surgery and as a result the negative pressure room was constructed. Shortly thereafter, the positive pressure method of maintenance of expansion of the lung was elaborated upon and perfected by Meltzer and Auer.<sup>10</sup> The principle involved, i.e., maintenance of lung inflation, was the same with both types of pressure, one working from within the air passages and the other from without. The method of Meltzer and Auer which made use of intratracheal anesthesia under positive pressure had considerable advantage over that of the negative pressure chamber in that it was much less expensive, much simpler of operation, and, therefore, lent itself for a wider usage. In spite of

Abb. 352. Erster primitiver Apparat zum Studium der Unterdruckwirkung nach Sauerbruch.

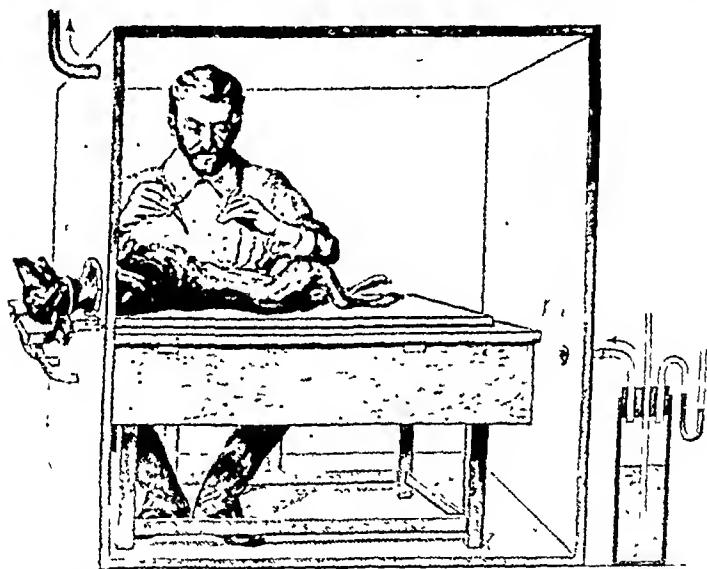


Fig. 1.—Negative pressure room developed by Sauerbruch for intrathoracic operations on animals. A similar room was constructed for clinical use. (After Sauerbruch.)

Meltzer's work and Elsberg's<sup>11, 12</sup> application of the same to clinical surgery, a state of confusion continued to exist regarding the detrimental effects of an open pneumothorax. During the flu epidemic of 1918 empyemas complicating the influenzal pneumonias were accompanied by an extremely high mortality when treated by early open drainage. The work of Graham and Bell<sup>13</sup> of the Empyema Commission of the U. S. Army presented seemingly irrefutable evidence that the risk of an open pneumothorax was directly proportional to the size of the opening in the chest wall. Sauerbruch,<sup>14</sup> of Germany, was a staunch believer of this point of view. On the other hand, Duval<sup>15</sup> in France felt that these dangers had been very much exaggerated. Clinical evidence in support of

and Bjorkman,<sup>18</sup> on examining the pulmonary ventilation of each lung independently using a method devised by Jacobaeus called broncho-spirometry, found that the respiratory function of the lung on the lower side of an unopened chest with a patient in a lateral position was greater than that of the upper side. This was thought to be due to an increased blood supply of the lower lung by gravitation. Although the experimental evidence appears irrefutable, the explanation for the results is not entirely convincing.



Fig 4A—X-ray of the chest of a 62-year-old woman who complained of a non-productive cough of several months' duration. The right upper and middle lung lobes were resected followed by an uneventful convalescence

Thus, in view of the many and varied difficulties and confusing ideas regarding this problem during even recent years, a very valid reason is obvious for the delay in making intrathoracic exploration a relatively safe procedure. The application of some of the principles developed within recent years will be discussed further under the heading of anesthesia

#### RESECTION OF LUNG TISSUE

The slow development of a suitable technique for lobectomy and pneu-

That the collapse of the lung which occurs during an exploratory thoracotomy is not in itself especially harmful, and does not reduce the normal lung capacity to a lethal level, has been repeatedly demonstrated. Both animals and human beings may well tolerate reduction in lung function to a marked degree; namely, one-third to one-sixth of their original capacity.<sup>17</sup> This fact is borne out by the frequent observation made during exploratory thoracotomy that the mobile mediastinum sinks well over the midline toward the unoperated side, thus impinging materially upon the function of the presumably normal lung. Fraenckner

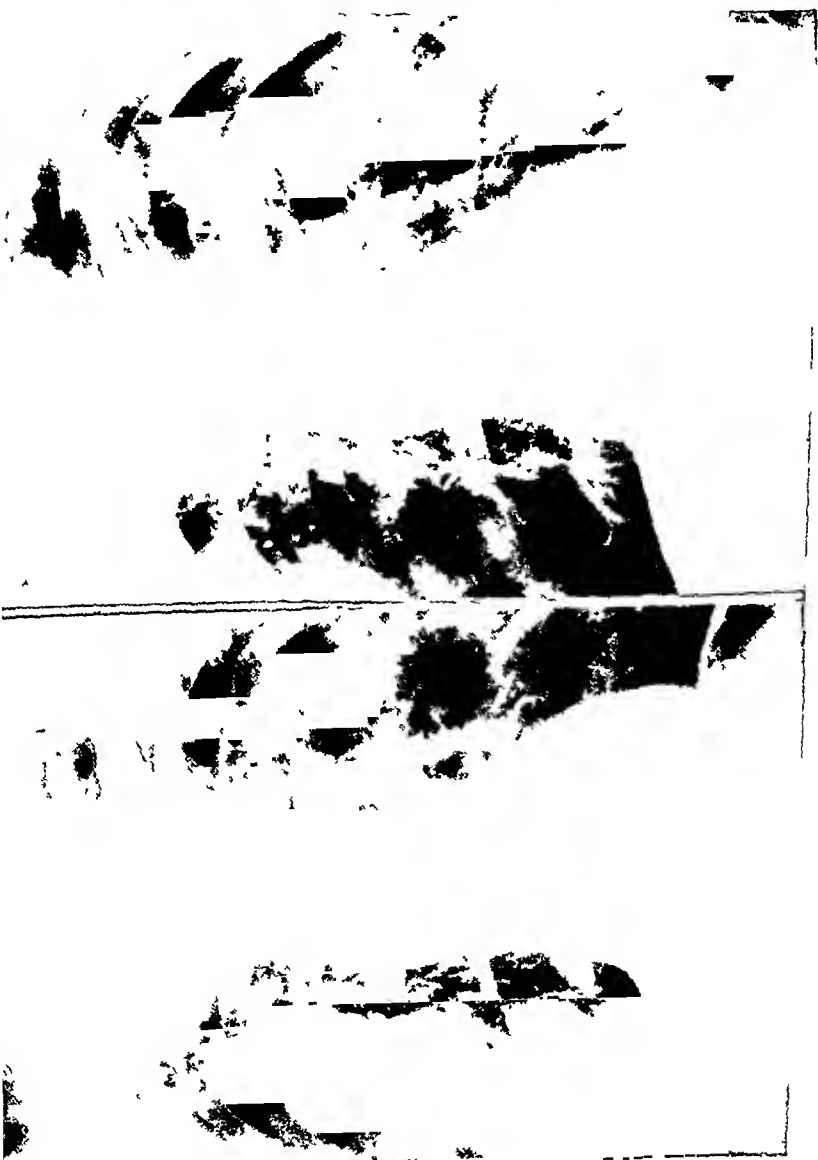


Fig 3—X-rays of the chest of a 53-year-old man taken before (A) and after (B) a one-year period. The patient was treated for tuberculosis for over one year until marked excavation of the tumor occurred. Rib resection and biopsy proved it to be a squamous-cell carcinoma of the lung.

Graham.<sup>23</sup> This has been explained in part as due to the lack of inherent healing in the bronchial wall by Bettman,<sup>24</sup> whose experiments were substantiated by others.<sup>25</sup> It was partly for this reason that mass ligation of the hilar structures was discarded in favor of the dissection technique. This consisted of individual ligation of the vessels and suturing of the bronchus followed by covering of the same with mediastinal pleura to encourage primary healing of the bronchial stump. More recently, compensatory changes following the reduction in lung function have been studied experimentally,<sup>26, 27, 28</sup> the results of which will be discussed under a separate heading.

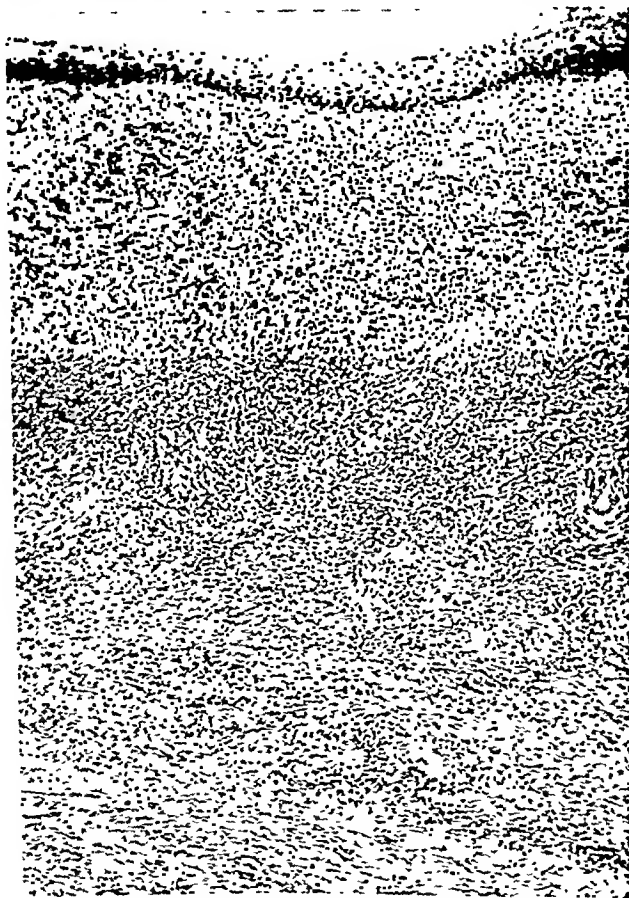


Fig 4C.—See opposite page for legend.

#### METHODS OF DIAGNOSIS

The third major factor in the delayed surgical treatment of primary lung tumors was the lack of diagnostic methods. With the discovery of x-ray by Roentgen<sup>29</sup> in 1895 and the subsequent development of an opaque medium, diagnosis of these tumors was much enhanced. The first successful use of the bronchoscope for removing foreign bodies from the

subject. The first total pneumonectomy was performed by Rolandus<sup>19</sup> in 1492. In 1881 Gluck<sup>20</sup> removed the entire lung on one side from six dogs and eight rabbits, of which two of the latter survived. Friedrich<sup>21</sup> in 1908, by use of the principle of dissection and separate ligation of vessels, was able to secure a favorable mortality rate in animals. Subsequently, with improvements in surgical technique, pneumonectomy in dogs has been carried out with less than 10 per cent mortality.<sup>22</sup>



B.

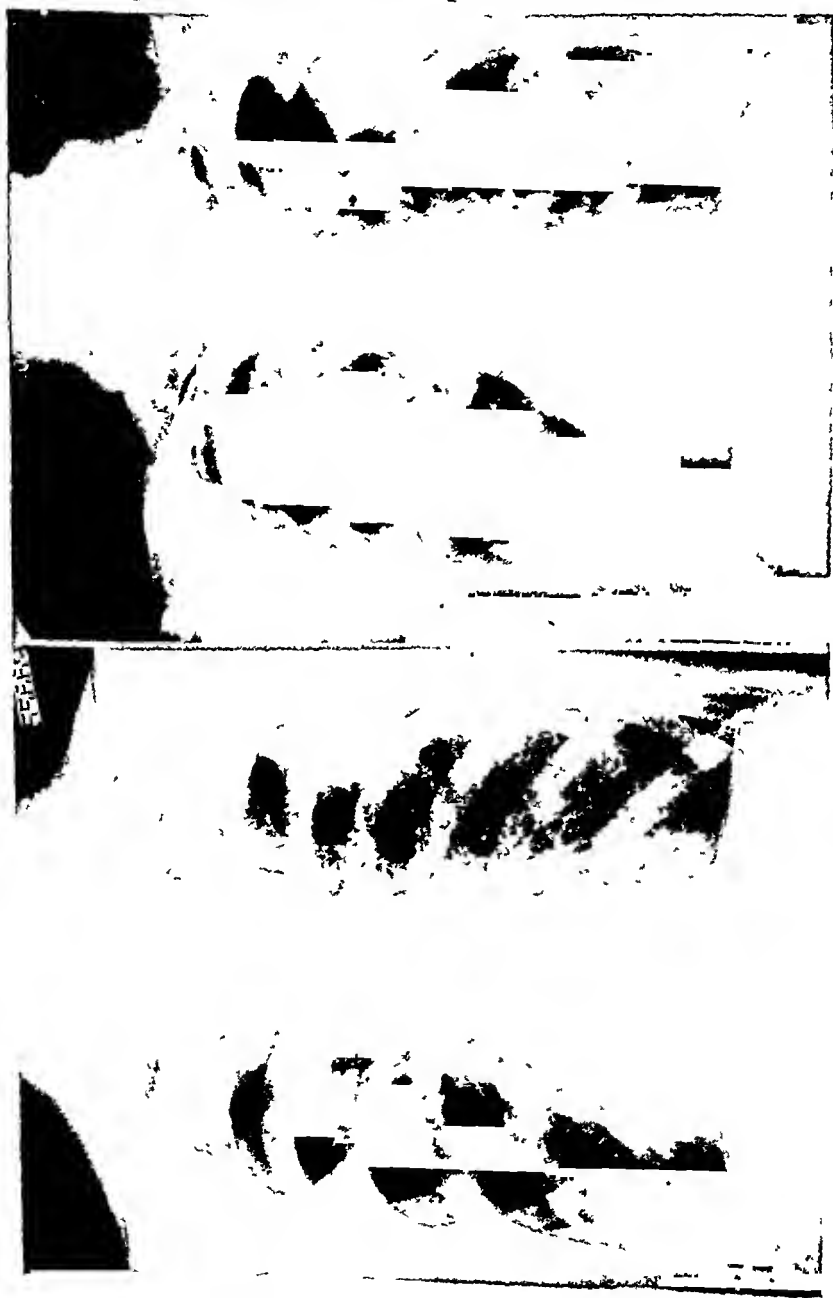
Fig. 4 B and C.—B. Microscopic section through entire tumor mass which consisted of a thick-walled cavity filled with pus. Guinea pigs injected with the contents of the cavity died of tuberculosis. Diagnosis: C. Photomicrograph (×120) of wall of cavity seen in B. Giant cells were found in some areas. C. Photomicrograph of wall of cavity seen in B. Giant cells were found in some areas. C. Photomicrograph of wall of cavity seen in B. Giant cells were found in some areas.

Lobeectomy for tumor and for bronchiectasis was accomplished as early as 1907 by Gluck whose results were later improved by Sauerbruch. Although the first pneumonectomy in animals was performed as early as 1492, the first successful pneumonectomy in man for tumor was not performed until 1933, almost four and one-half centuries later, by

in methods of diagnosis it has been found to rank second in frequency only to carcinoma of the stomach.<sup>31</sup> Thus, it is now appreciated as one of the major problems in the treatment of neoplastic disease.

#### CLASSIFICATION OF TUMORS

A discussion of the recent advances in the surgical treatment of primary lung tumor would be incomplete without some attention being



D.

Figs 5C and D—See opposite page for legend.

air passages made by Killian<sup>30</sup> in 1897 was another great step forward not only in the establishment of a correct diagnosis during an earlier stage of the tumor but also in the realization of its frequent occurrence. Whereas primary malignant tumor of the lung was once thought to be infrequent and of interest chiefly to the pathologist, with improvement

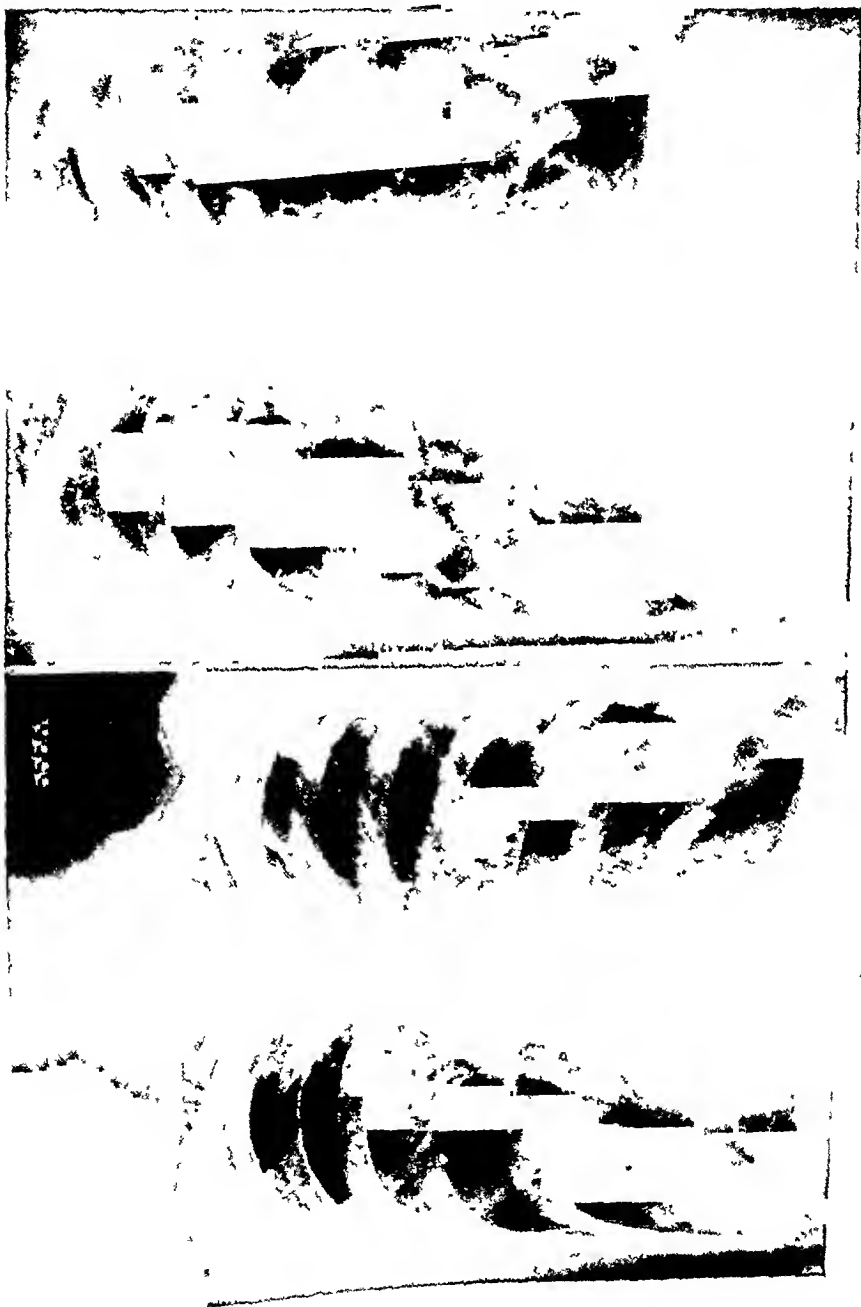
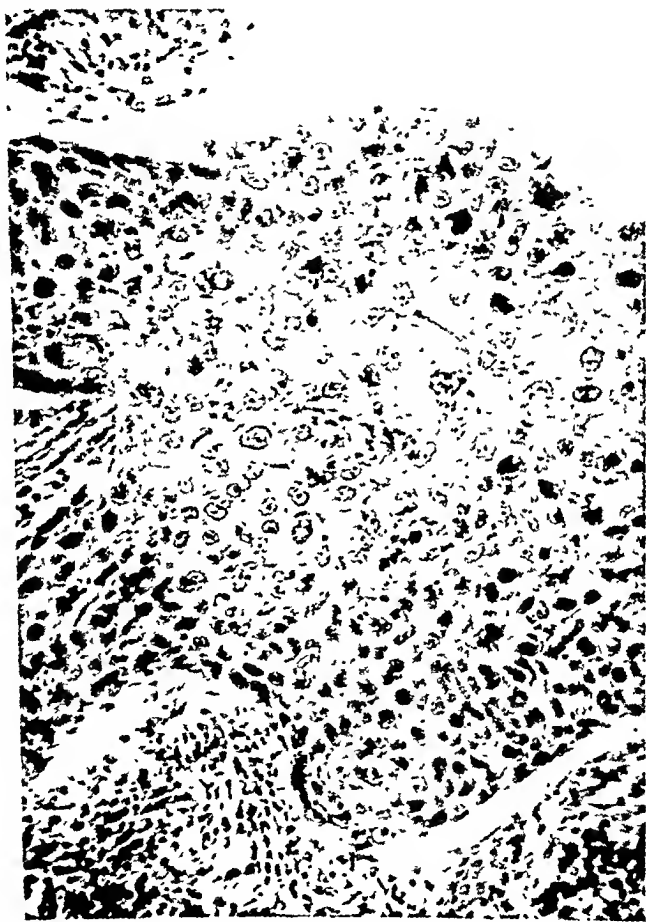


Fig. 54-D—Four x-rays of the chest of a 57-year-old male taken on the respective dates April 5 1937 Aug 1, 1935, Dec 11, 1939, and April 10, 1941, thus over a period of four years. The patient was first seen because of asthma the wheezing. He was entirely asymptomatic when the last x-ray was taken. Note gradually enlarging opacity in second right interspace anteroposteriorly.



ment which persists between various authors in this regard is probably best explained by the marked variation in both the rate of growth and the cell type and arrangement in different tumors. If one is to take evidence of infiltration of surrounding structures, as well as metastases to neighboring lymph nodes and distal tissues and organs as a criterion of malignancy, the length of the clinical course may vary from one to fifteen or twenty years. Naturally this variation in clinical course and histologic appearance has had considerable influence on previous methods of treatment prescribed.



F

Fig. 5F—See opposite page for legend

Again, the location of the tumor may vary from a main stem bronchus to the extreme periphery of the lung, whether it be a squamous-cell or some other cell type of carcinoma. The location of the tumor is likely to have a definite bearing not only on the clinical course but on the stage at which a correct diagnosis is made. In general, symptoms are manifested earlier in tumors located in the primary stem bronchi, due to irri-

given to the variety of tumors involved. For all practical purposes, primary malignant tumor of the lung is synonymous with bronchogenic carcinoma. Other tumors such as sarcoma, endothelioma, etc., can be dismissed as being rare since the variation in cell type and pattern of arrangement in bronchogenic carcinoma has been recognized. As stated above, during recent years the incidence of this tumor has been shown



E.

Fig. 5 E and F.—Microscopic section (E) and photomicrograph ( $\times 325$ ) (F) showing a squamous-cell carcinoma of the lung.

to rank second only to that of carcinoma of the stomach. This represents approximately 10 per cent of all malignant tumors. (Seyforth,<sup>32</sup> Jaffé,<sup>33</sup> Koletsky,<sup>34</sup> Simons,<sup>35</sup> Overholt.<sup>36</sup>)

A universally accepted classification of bronchogenic carcinoma is not in existence at the present time. Various classifications have been presented from time to time and more recently by Tuttle and Womack,<sup>37</sup> Halpert,<sup>38</sup> Rabinovitch and associates,<sup>39</sup> and Gebauer.<sup>40</sup> The disagree-

given by Rabinovitch, Hochberg, and Lederer.<sup>39</sup> These authors classify bronchogenic carcinoma into three main groups as follows:

1. Squamous cell carcinoma
2. Cylindric-cell carcinoma which includes
  - a. Adenoma
  - b. Undifferentiated cell carcinoma, including
    - (1) Medullary
    - (2) Round cell
    - (3) Oat cell
3. Pleomorphic-cell carcinoma



Fig. 6.1—X-ray of chest of a 62-year-old woman who complained of a productive cough, repeated hemoptyses, and attacks of pneumonia over a period of several years' duration. Note triangular-shaped opacity in lower right lung field due to atelectasis and pneumonitis.\*

They state that the unicellular theory seems to hold true and explains the various forms of malignant growth that may arise in the bronchial tree. A fourth classification has been presented by Tuttle and Womaek in collaboration with Graham<sup>17</sup> which divides all tumors into two groups; i.e., squamous-cell carcinoma and mixed tumors of the lung. These authors have presented evidence that various cell types and arrangement of the same may be found within the same tumor and that many apparently benign tumors are actually malignant, as demonstrated by metastases in the lymphatics and by invasion of adjacent structures.

tation of the mucosa and to the development of infection subsequent to obstruction of the air passages. This centrally located group represents about 75 per cent of all bronchogenic carcinomas and has been thought to be the most favorable group for surgical treatment inasmuch as an earlier diagnosis can be established from bronchoscopic examination and biopsy. Indeed, tumors located near the periphery may become several centimeters in diameter only to be found accidentally on x-ray examination before any symptoms have been noted. Again, tumors may become quite large, the center may become necrotic with cavity formation giving rise to the symptoms and signs of lung abscess as the first evidence of the presence of a tumor. In a recent report by Hauser and Wolpaw<sup>41</sup> this course represented about 12 per cent of all bronchogenic carcinomas. Still another group of tumors arising in the main stem bronchi and projecting both into the bronchial lumen and infiltrating the peribronchial structures gives rise to repeated attacks which are diagnosed as pneumonia, the attacks usually extending over a period of several years.<sup>42</sup> This group of tumors has been called benign bronchial adenoma as well as numerous other names, but from the standpoint of cellular structure the benign cannot be differentiated from the malignant variety. Churchill<sup>43</sup> states that this group represents about 5 per cent of all bronchogenic carcinomas.

Purely benign tumors of the lung are relatively rare and include chondroma, lipoma, fibroma, and angioma. These tumors need little consideration since they represent such a small minority of primary lung tumors. Another relatively nonmalignant tumor is the endothelioma, four of which were recently reported by Edwards and Taylor.<sup>44</sup> These tumors, along with the above-mentioned benign tumors, produce symptoms either by pressure upon adjacent structures or by secondary infection of the bronchial tree due to obstruction. An angioma of the lung treated by Tuffier<sup>45</sup> in 1889 involved the chest wall, eroding the ribs by pressure. A number of angiomas have been removed by Sauerbruch.<sup>46</sup> One characteristic of thoracic angiomas, as is common with angiomas elsewhere, is the marked hemorrhage which usually occurs with their removal. This may be serious and is usually controlled by suture and packing.

Primary carcinoma of the lung has received various classifications, the following of which have been most recent: Halpert<sup>38</sup> has divided them into three types, depending upon the embryological direction of growth: (1) the "reserve-cell" carcinoma, (2) cylindrical-cell carcinoma, and (3) squamous-cell carcinoma. He believes that all tumors arise from one cell; namely, the basal cell. Ochsner and DeBakey<sup>47</sup> find this to be the most logical classification of primary carcinoma of the lung. Gebauer<sup>40</sup> divides bronchogenic carcinoma into three fundamental types; namely, small-cell carcinoma, adenocarcinoma, and squamous-cell carcinoma. He believes that this tumor "cannot be regarded pathologically or clinically as a single entity." A third classification is that

tumor. To a lesser extent symptoms are produced by direct invasion of adjacent structures. On the other hand, many tumors located in the peripheral portion of the lung remain quiescent for months or even years, regardless of the type of tumor cell or their arrangement (Fig. 5). Again, as mentioned above, central necrosis with cavity formation and infection in some tumors produces symptoms and signs of pulmonary suppuration, tuberculous or nontuberculous in nature. Most of these features have been discussed by others<sup>41, 48</sup> and need not be given detailed discussion here. It will be apparent at once that the sooner symptoms



C.

Fig. 4C.—See opposite page for legend.

are produced by a tumor, the greater the likelihood that an early diagnosis will be made, providing diagnostic methods are properly used. Thus, tumors which remain "silent" and are found only late in the course of the disease will have a much poorer prognosis, providing their degree of malignancy is the same.

One of the principal factors in diagnosis is suspicion of the presence of a tumor. Over 40 years of age having symptoms referable to the lung, the high incidence of the tumor is kept in mind,

Thus it is quite apparent that a uniform opinion regarding the pathologic characteristics of bronchogenic carcinoma does not exist at the present time. This, in the past and to some extent also at the present, has added greatly to the confusion regarding the early diagnosis and proper therapy for these tumors. It is quite probable that the unicellular theory is correct and that the rate of growth and degree of malignancy is variable regardless of the type of cells or their arrangement. What is more important is that these tumors are all potentially malignant and should be treated as such, following the principles for treatment of carcinoma elsewhere in the body; namely, the complete removal of all of the tumor-bearing tissue. When considered from this aspect an earlier diagnosis may be expected, and proper therapeutic measures may be instituted at a time when the tumor is still in the operable stage.



B.

Fig. 6 B and C.—Photograph of resected right lower lobe (B) and microscopic section (C) through entire specimen. Note bronchial tumor filling a secondary bronchus and extending out into the primary bronchus of the lobe. The completely obstructed portion of the lung is atelectatic, the incompletely obstructed portion is bronchiectatic.\*

#### DIAGNOSIS

The clinical symptoms and physical findings in bronchogenic carcinoma are extremely variable, not only in different patients but at different periods in the same patient. Statistics covering this feature should not be gathered from all tumors as one group, nor from all stages of the tumor, for this would be very misleading. In general, one can say that a large proportion of the symptoms are on the basis of infection of the respiratory passages due to varying degrees of obstruction by the

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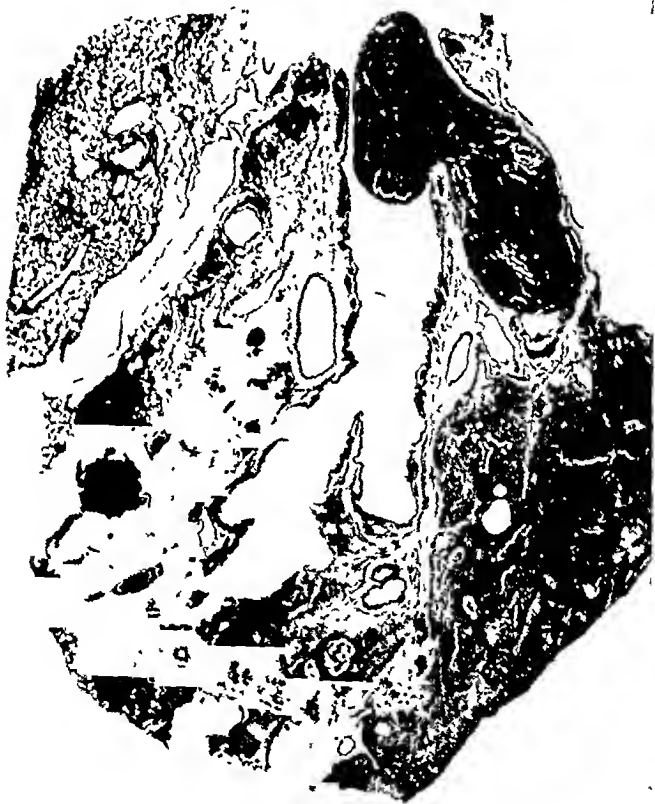


Fig. 6C—See opposite page for legend

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*Differential Diagnosis.*—One of the most difficult conditions to be differentiated from peripherally located carcinoma is pulmonary tuberculosis. As already pointed out by Hauser and Wolpaw, cavitation occurs in about 12 per cent of the tumors and both roentgenologically and clinically may simulate the appearance of pulmonary tuberculosis (Fig. 3). Again, one may occasionally see a solitary tuberculous lesion which produces an opaque shadow on x-ray examination and which appears not unlike a peripherally located primary lung tumor (Fig. 4). In the later stages of the tumor, empyema and nontuberculous lung abscesses are often presented as the primary diagnosis. Again, in the more benign, centrally located tumors due to the presence of infection of the air passages, bronchiectasis and repeated attacks of pneumonia are commonly mistaken as the primary diagnosis. Thus it is evident that when these lesions occur in patients where primary carcinoma is likely to be found an early differentiation can be made only by observation and by the use of available diagnostic methods.<sup>51, 52</sup>

*(To be concluded in the December issue. The references will accompany the last section.)*

a search will be rewarded by a higher percentage of early diagnoses. If fluoroscopic examinations were made as a routine at regular intervals on all patients in this group, a higher percentage of the peripheral lung tumors would be diagnosed at an earlier stage thus improving the prognosis for the group. For the centrally located variety, bronchoscopic examination and biopsy of the tumor in all patients with unexplained cough would give rise to an early diagnosis, even before x-ray evidence is demonstrable.

Other diagnostic methods which are available include examination of the sputum as described by Dudgeon<sup>19</sup> for malignant cells which give a positive finding in a high percentage of patients where tumor cells are present in the sputum. This is especially applicable to tumors located peripherally with necrosis of the central portion. There is also available examination of pleural effusions by Mandelbaum's method<sup>50</sup> which



Fig. 6D.—*Left*, Photomicrograph ( $\times 27$ ) showing intrabronchial tumor with its surface layer of fibrous tissue covered by stratified squamous epithelium and at the upper left a layer of fibrin infiltrated by leucocytes. *Right*, Photomicrograph ( $\times 560$ ) showing the character of the tumor cells and their stroma.\*

includes centrifugation and fixation of the sediment with subsequent staining for microscopic examination. Both of these diagnostic methods are usually positive only after the tumor has progressed beyond the operative stage. A third diagnostic procedure which has been reported of value by some authors is aspiration biopsy. Here again, its application is only in peripherally located tumors and is likely to be made after the tumor has become inoperable. The advisability of its employment is questionable since spread of the tumor along the path of the needle puncture has been frequently observed. Since bronchoscopic examination with biopsy of tumor tissue is applicable to about 75 per cent of all primary carcinoma, it remains the most valuable procedure for improving surgical treatment.

the blood pressure returned to normal and had remained so for two and fifteen years, respectively, after cystoscopic destruction of the ureterocele.

W. H. Toulson, Baltimore, reviewed 41 perinephric abscesses, of which 13 were secondary to renal suppuration, 27 were apparently primary, and 1 was an extension of inflammation from an adjoining viscus.

G. C. Prather, Boston, studied 72 cases of pyelonephritis of pregnancy, 40 per cent of which recurred in subsequent pregnancies. He could not detect any increased tendency to hypertension in subsequent pregnancies; i.e., a patient who has had a pyelonephritis is no more likely to have hypertension than one who has not.

J. K. Ormond, Detroit, lavaged the renal pelvis with 25 per cent silver nitrate for an acute pyelonephritis. Nine years later nephrectomy was done for a pyonephrosis with an impassable ureteral stricture, and deposits of silver were demonstrable in the interstitial tissue. Destruction was attributed to extravasation of the silver nitrate into the parenchyma.

D. M. Davis, Philadelphia, presented a cystoscopic table with a top and leg holders which could be slid up away from the Bucky diaphragm and over a fluoroscopic apparatus, without disturbing the patient.

The following papers were presented on May 30:

A. J. Scholl, Los Angeles, reviewed 6 cases of gunshot wounds of the kidney seen in ten years, and concluded that the injury of the kidney was usually secondary in importance to that of the intestines, wounding of which often led to death.

A. L. Dean, Jr., New York City, declared that no satisfactory routine for the treatment of Wilms's tumors of the kidney has been established. The tumors are capricious in their response to irradiation, after which they always recur. Irradiation followed by nephrectomy is the most satisfactory treatment thus far available, 2 of his patients so treated being well for four and one half years.

G. W. Fish and G. F. Cahill, New York City, had records of 58 cases of polycystic kidneys. Twenty three came to operation (drainage of cysts, abscesses, nephrectomy for complicating tumors, etc.), of which 17 were living and apparently well for from one to sixteen years.

G. G. Smith, Boston, discussed the indications for ureteroenterostomy, basing his conclusions on 54 patients. The surgical mortality should be below 15 per cent. Late complications are rather frequent, and the utility of the operation in cancer of the bladder is still debatable. He employs unilateral extraperitoneal transplantation without catheters.

F. H. Colby, Boston, advocates cutaneous ureterostomy in tuberculosis involving both kidneys or a solitary kidney in the presence of intolerable cystitis. If a satisfactory projection of ureter beyond skin can be arranged, catheters can be omitted and modified colostomy cups used. In 10 cases gratifying relief was secured.

C. D. Creevy, Minneapolis, described 4 unusual examples of obstruction at the ureteropelvic junction including 1 granuloma, 3 polyps, and 1 recurrent obstruction above the ureteropelvic junction by accessory vessels deliberately left at operation. He concluded that the junction should always be explored during plastic operations, and that accessory vessels should always be divided.

Alexander Randall, Philadelphia, reported a tumor of the ureter which was diagnosed by urography and treated by nephroureterectomy, but which proved to be an endometrioma on section.

# Review of Recent Meetings

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## REPORT OF THE MEETING OF THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS, HOT SPRINGS, VA.

MAY 29-31, 1941

C. D. CREEVY, M.D., MINNEAPOLIS, MINN.

*(From the Department of Urology, University of Minnesota Medical School)*

THE FIFTY-THIRD annual meeting of the American Association of Genito-Urinary Surgeons was held in Hot Springs, Va., May 29, 30, and 31. The meeting opened on May 29 with the following papers:

W. J. Engel, Cleveland, reported two cases of pheochromocytoma of the adrenal. In each there was a variable but not paroxysmal hypertension, with symptoms suggesting hyperthyroidism. One patient had a severe diabetes and died from an infection, the tumor being discovered at necropsy. The second patient, a 19-year-old girl, had attacks characterized by a feeling of intense heat, followed by faintness and perspiration. Pyelography and perirenal air insufflation were not diagnostic; the tumor was discovered at exploration; recovery followed its removal. The importance of adrenalin and transfusion during and immediately after operation was stressed.

B. H. Hager, Los Angeles, added to the meager literature another example of an apparently solitary metastasis from a renal neoplasm. A tumor of the left chest wall of eight years' standing proved, on excision, to be a renal carcinoma. Pyelography incriminated the left kidney which was removed a month later. Twenty-five months after operation the patient was well.

G. S. Foulds, Toronto, Ontario, described a neoplasm of the kidney which in some areas was a papillary cystadenocarcinoma, in others a hypernephroma, and in still others intermediate between the two.

H. G. Bugbee, New York City, presented a case of renal tuberculosis in which the pyelogram was that of a papillary neoplasm of the renal pelvis. This was due to a tuberculoma.

W. C. Quinby, Boston, discussed current theories which attribute some hypertension to local renal disease, and reported experiments in which a temporary rise of systemic blood pressure followed temporary occlusion of the renal artery in animals with vagi cut, heart denervated, and adrenals removed. This he regarded as proof that the mechanism of hypertension is "humoral."

V. J. O'Connor, Chicago, reported two very interesting examples of hypertension in young men, each with a solitary kidney, hydronephrosis, and ureterocoele. In both,

Received for publication. July 28, 1941.

R. M. Nesbit and R. H. Cummings, Ann Arbor, Mich., found that the routine use of prostigmine in patients with postoperative urinary retention was ineffective. Given prophylactically, it apparently did prevent retention in a small percentage of cases.

H. G. Hamer, Indianapolis, presented the case of an unusual prostatic abscess, which was small, centrally located, and which was mistaken for a benign hypertrophy by several examiners. The patient died of cardiac failure and pneumonia, and the abscess was found at necropsy. It had not been influenced by sulfanilamide.

W. N. Wishard, Jr., Indianapolis, reviewed the subject of carcinoma of the male urethra, 171 of which are reported in the literature, 20 since 1938. He concludes that its frequency is increasing. His patient had a transitional cell carcinoma of the penile urethra near the external meatus, five years after fulguration had cured a papilloma of the membranous urethra. Radon and x-ray apparently destroyed the tumor, the patient now being well (except for a stricture) for two years.

W. J. Baker, Chicago, resected a vesical neoplasm which proved to be an endometriosis.

M. L. Boyd, Atlanta, Ga., discussed an ulcer of the bladder which led to hydronephrosis and refused to respond to protracted conservative treatment. It was resected and found to be inflammatory, presumably from infection with *Streptococcus faecalis*.

C. F. Rusche, Hollywood, Calif., reviewed two vesical neoplasms which on removal were seen to consist of deposits of amyloid in areas of chronic inflammation. Such solitary deposits have been found in other organs but cannot be explained satisfactorily.

Leon Herman, Philadelphia, discussed several unusual urological cases, chief among which were a scrotal metastasis from a carcinoma of the stomach and a testicular metastasis from a carcinoma of the bladder.

On May 31, the following papers were presented:

H. C. Bumpus, Jr., Pasadena, Calif., discussed the treatment of carcinoma of the prostate and concluded that transurethral resection of obstructing tissue gives the patient more comfort than any other single method. Symptomless carcinomas are best let alone; the radical operation, because of its limited applicability, the likelihood of distant metastases from a small primary, its high mortality, and difficulties in accurate microscopic diagnosis, offers no advantages.

W. P. Herbst, Jr., Washington, D. C., recounted his experience with estrogens in the treatment of prostatic carcinoma. Seven patients were treated, all with apparent benefit, especially in the relief of pain from metastases. Whether the benefit results from depression of the anterior pituitary or of the testes is not known.

C. M. Johnson and Frank Hinman, San Francisco, and J. M. Carr, Stockton, Calif., have abandoned the so-called radical orchidectomy because crossed lymphatic metastases defeat its purpose so frequently. Since 1936, they have subjected 44 testicular neoplasms to simple orchidectomy followed by irradiation. All patients who had increased urinary prolans are dead, the longest survival being fifteen months. Twenty-three of 30 with normal prolans are living fifteen to seventy-two months. The Friedman (rabbit) test for prolans is too insensitive to be of value in testicular neoplasms.

R. C. Graves, Boston, and K. B. Lawrence, Wrentham, Mass., resorted to castration and irradiation of a patient with bilateral testicular neoplasms and palpable abdominal metastases. Although the masses disappeared, the patient died in a few months.

N. J. Heckel, Chicago, observed that alpha-estradiol (progynon) administered to patients with benign prostatic hypertrophy caused enlargement of the breasts, degeneration of the testes (aspiration biopsy), disappearance of the seminal fluid, aspermia and impotence, but did not affect the size of the prostate nor its symptoms.

B. S. Barringer, New York City, called attention to the value of the subarachnoid injection of absolute alcohol in controlling the pain of apparently hopeless cancer. In 3 instances, the disappearance of pain turned the tide in the patient's favor, and the tumor was then controlled by irradiation with seeming restoration of normal health.

work supplies some concrete facts about the effects of six months' physical training on raw recruits in the South African Army

The results reported on the thirty two young men are of great interest and their implications are of first rate importance. The alterations in posture and physiognomy are striking. Together with the changes recorded in the performance tests, they provide a powerful argument for physical training for all young men. The authors exhibit justifiable gratification at the amount of work they accomplished in this study, but they should be the first to agree that they have only pointed the way to much more exhaustive studies. They have not touched the question of "efficiency" in the physical or chemical sense and the whole field of metabolic alterations is left blank. Such practical matters as the kind of physical training regime best suited to promote the desirable alterations are not mentioned. Recognition of the limitations of the present work is not to detract from its virtues but simply to indicate that the social importance of such problems merits the efforts of dozens of other groups.

The book itself is a curious mixture of appeal to popular understanding and of scientific data presented in rather tedious garb. Careful reading, or rather study, is necessary to keep track of the relative changes in the numerous sub groupings of the men "best performers," "poorest improvers," etc. The presentation of all data in extenso detracts from the text though the flagging interest of the reader is revived from time to time by amusing pencil drawings depicting the conversion of the puny and aimless loafer to the stalwart young man who is an asset to himself and his community. The references are not numerous but cover a fair sample of recent material of relevance. We can commend the work to the thoughtful consideration of physicians, educators, and government administrators alike and hope that Joki, Claver, and their colleagues will continue their valuable studies in this field.

**Sulfanilamide and Related Compounds in General Practice** By Wesley W Spink  
Ed 1 Pp 256 Chicago, 1941, Year Book Publishers, Inc \$3

This volume concerning sulfonamide therapy is the best published to date. The first chapter gives a short historical review, the subsequent chapters deal with the indications and results of treatment with the different sulfonamide compounds. The author writes from a wide clinical experience, his evaluations are sound, his enthusiasm temperate, and his review of the pertinent literature critical and concise. An extensive bibliography and a workable index are appended. Every doctor who wishes to have the latest knowledge concerning sulfonamide therapy should read this book.

**The Treatment of Cancer and Allied Diseases (3 volumes).** By George T Pack and Edward M Livingston Ed 1 Pp 2598, with 1,500 illustrations New York, 1941, Paul B Hoeber, Inc \$36

Without question, these are the best composite group of volumes published on the management of malignancy to date. A number of years ago Zweifel and Payr edited a similar three volume work on the malignancy problem. However, the present work written by 147 authors, largely American, under the editorial supervision of Pack and Livingston, is a far superior collection of monographs, from the standpoint of the clinician. Written by leaders in their respective fields, these books, covering systematically the treatment of all body malignancies, present the best accomplish-

# Book Reviews

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**Body Mechanics in Health and Disease.** By J. L. Goldthwait, L. T. Brown, L. T. Swain, J. C. Kuhns, and W. J. Kerr. Ed. 3. Pp. 316, with 121 illustrations. Philadelphia, 1941, J. B. Lippincott Co. \$5.

This volume is essentially a study of chronic diseases associated with faulty body mechanics. The authors are recognized experts in their fields of orthopedic surgery or internal medicine, but it may be questioned how acceptable some of the statements would be if less well known writers had published this book. Certain statements are not only illogical but are lacking in proof. For instance, on page 104, could not "rest" alone, and not "the correction of the faulty body mechanics" have helped the heart failure in the patient with chronic valvular disease? On page 108, the description of the type of individual with hypotension is not statistically verified. There is too much armchair thinking in the discussion of anatomy and diseases of the duodenum (page 141) and small intestine. Most of the illustrative cases concerning the effect of posture on certain visceral disturbances impressed the reviewer as being incomplete and inconclusive.

Throughout the book, too much emphasis is placed on the role of body mechanics in the treatment of disease. May not faulty body mechanics be more often the result rather than the cause of certain physical disorders?

Some considerations concerning corrective and preventative treatment of faulty posture are given. An extensive bibliography and a workable index are appended. The binding and printing of the book are excellent.

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**Training and Efficiency. An Experiment in Physical and Economic Rehabilitation** By E. Jokl, E. H. Cluver, C. Goedvolk, and T. W. DeJongh. Pp. 188. Johannesburg, South Africa, 1941, The South African Institute for Medical Research.

On the flyleaf of this book there appears a quotation which is not merely the keynote of the present book but which also represents the fundamental orientation of the work of the Johannesburg group. The quotation is from Professor John Ryle's opening address to the students of the Cambridge Medical Faculty on Oct. 15, 1940:

"By one means or another you must develop the social conscience, which has, in the view of many of us, been too little evident in the years preceding the war. Although there have always been noble and notable exceptions in every community it has seemed to me that medical students and doctors as a body, excusing themselves on the grounds of their many preoccupations with the curriculum or the anxieties of practice, have held themselves too much aloof from the larger social problems."

It is logical that the social responsibility of medicine must begin with scientific consideration of the physiology and anatomy of the individual. The obvious second step is to inquire into the influence of mode of life and environment on the individual as a functional machine and as a citizen. Such questions have been the subject of innumerable treatises "about it and about," but usually eloquent verbiage and argument have had to suffice in place of concrete material fact. The present



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## Original Communications

### THE MECHANISMS OF GASTRIC SECRETION\*

A. C. IVY, PH.D., M.D.,† CHICAGO, ILL.

THE problem of the mechanisms of gastric secretion is of obvious academic interest. From the clinical viewpoint it is of interest because when we know the mechanisms of a biologic process, we usually are able to understand and to control variations from the normal, or to make an etiological diagnosis and to apply etiological therapy. Or, to express the idea more simply, situations arise clinically in which we should like to turn gastric secretion on or off at will. At the present time we have to be satisfied with neutralizing and buffering the secretion, or reseeding the acid-secreting portion of the stomach, or replacing the water and acid chloride lost externally by water and salt given by clysis. At least we should find some harmless way to turn off a hypercontinuous secretion. Dr. Judd stated the problem just that way to me some twelve years ago when I was telling him of some of the academic questions pertaining to gastric secretion which I was studying. Since that time we have made some progress.

The subject of the mechanisms of gastric secretion is at present complicated because certain important questions cannot be answered. When these questions are answered, the subject will be relatively simple and can be outlined on one or two typewritten pages. *Because the subject is now complicated, I suspect that portions of it cannot be understood by the uninitiated without careful study.* There are portions of the subject that are rather simple and clear.

It will be noted that in the physiologic approach to this problem, the physiologist must resort to the use of surgical methods, without the successful use of which progress in this field could not occur.

It is best to approach this subject by outlining the periods and phases of gastric secretion. For the most part these are well established and recognized.

\*The eighth E. Starr Judd Lecture, presented on Jan. 15, 1941, at the University of Minnesota Medical School, Minneapolis, Minn.

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ments in the cancer problem. The surgical, as well as the irradiation aspects of treatment, are presented. A unique feature of the volumes, new to this reviewer, is a repelative discussion of technical procedures by authors, employing somewhat dissimilar approaches to the same problem. For instance, in Volume II, the reader, interested in informing himself on the best current opinion on the surgical treatment of cancer of the rectum, will find chapters written by such men as Jones, Rankin, Lahey, Babcock and others, each detailing the features of his particular operation.

These volumes constitute a real addition to the literature of the treatment of malignancy and will be found eminently useful and practical by radiologists and surgeons alike.

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**Field Surgery in Total War.** By Douglas W. Jolly. Ed. 1. Pp. 242, with 32 illustrations. New York, 1941, Paul B. Hoeber, Inc. \$3.50.

The special feature of this book, which particularly recommends it, is that it is written by a surgeon just fresh from an active surgical service in war; viz., the recent Spanish Revolution. The first section of the book deals with organization and tactical disposition of surgical units in the field. The author is an ardent supporter of the "three point forward system." This scheme embraces a casualty classification post for the proper division of cases; a No. 1 Hospital for the most urgent cases, and a No. 2 Hospital for the less urgent cases with sector evacuation and Base Hospitals in the rear.

The subject matter of surgical treatment of war wounds of the various parts of the body is treated in an orthodox fashion. The chief weakness of the book lies in the failure to mention or discuss the types of injury inflicted by the various implements of war. Certainly such a discussion might reasonably be expected to be found in such a text. Similarly, additional illustrations would augment the value of the text. Within the space of 240 pages, the author has succeeded in compressing a large broad personal experience with war wounds. It is a worth-while manual for surgeons, interested in the casualties of war, to study.

"psychic" secretion of Pavlov), which are dependent on the integrity of the cerebrum, and by (B) *unconditional reflexes*, which are not dependent on the cerebrum. An unconditional reflex stimulation of gastric secretion is analogous to the unconditional secretion of saliva when acid is placed in the mouth. The conditional reflex stimulation of gastric secretion is analogous to the conditional secretion of saliva when a bell is rung, or when one thinks of food or sees food. Zeligy<sup>8</sup> has reported that decorticated dogs do not secrete in response to the sight and smell of food, but do respond when they are "sham fed." "Sham feeding" consists of feeding an animal with an esophagostomy; the masticated and swallowed food does not enter the stomach.

The vagi contain the excitatory nerves for the cephalic phase of gastric secretion; they also contain inhibitory nerves. The splanchnic nerves gastric secretion. They do not conduct any of the nerve impulses responsible for secretion in sham feeding. They may, however, conduct impulses which stimulate secretion under other conditions, though this has not been demonstrated.

TABLE I  
AMOUNTS OF JUICE FOR EACH PHASE

PERIOD OR PHASE	DOG		MAN	
	NORMAL (C.C.)	ABNORMAL (C.C.)	NORMAL (C.C.)	ABNORMAL (C.C.)
Continuous	0.5-4/hr.	10-30/hr.	30-60/hr.	100-360/hr.
1. Cephalic	10-75/20 min.	500-700 in 4-6 hr.*	50-150/20 min.	?
2. Gastric phase	100-250/5 hr.		225-350/5 hr.	?
Mechanical	20-50/30 min.	?	?	?
Secretagogues	20-40/30 min.	?	?	?
Liver extract				
3. Intestinal phase	200-300/12 hr.	600-650/24 hr.†	225-350/5 hr.?	

\*Sham feeding for 4 to 6 hours, exceptional cases. Maximum rate of secretion I have observed in man is 11 c.c. per minute. Maximum rate of secretion I have observed in dogs is 4 c.c. per minute.

†Pylorus blocked and feeding via duodenal fistula (Webster and Armour). We have obtained from 500 up to 1,500 c.c. of juice in 24 hours from enterectomized dogs, with gastric catheter and 400 c.c. Ringer's solution every 6 hours. Atropine markedly reduced (about two-thirds) the volume of secretion. Operations in the upper abdomen stimulate gastric secretion; why, is unknown. We believe it is a "traumatic secretion" due to absorption of secretagogues, such as histamine. It does not take much histamine to stimulate gastric secretion, much more is required to produce shock, a condition in which secretion of acid does not occur.

The amount of juice (Table I) resulting from the cephalic phase is subject to considerable variation in the same subject. This phase is prevented by atropine as well as by section of the vagi.

Some surgeons, when performing a partial gastrectomy for peptic ulcer, have sectioned one or both vagus nerves to annul the cephalic phase of gastric secretion. The value of the procedure in the treatment of ulcer is mooted.<sup>9, 10, 11</sup> The procedure will, if the vagi are completely sectioned, annul the cephalic phase and reduce the total secretion of gastric juice in response to a meal. The efficacy of the vagotomy in the therapy of ulcer will depend on the extents to which the cephalic phase contributed to the patient's total gastric secretion, to which the

## PERIODS AND PHASES OF GASTRIC SECRETION

Gastric secretion may be divided into two periods:

*Period I. The Period of Interdigestive or Continuous Secretion.*—This is the secretion that occurs in the absence of food from the stomach.<sup>1</sup> Its amount and acidity vary. It is present in variable amounts throughout a fast of forty days.<sup>2</sup> Its existence was not recognized by Pavlov<sup>3</sup> because he thought the resting or empty stomach does not secrete acid, and that if acid is present, it is due to the thought of food. Yet, unless one recognizes that the empty stomach does secrete acid at periods, one will erroneously interpret the occurrence of a “spontaneous” secretion after the introduction of an experimental procedure as evidence of stimulation.

In experimental work on man and animal the continuous secretion should be collected for a period before any procedure is introduced, and the fact should be kept in mind that a small increase or decrease may be spontaneous. It is also important under certain conditions to observe the recovery of the secretory mechanism of the stomach after it has been stimulated. Sometimes after the stomach has emptied, it continues to secrete abnormal amounts of acid.

Some patients, particularly those with a duodenal ulcer, manifest a “hypernormal continuous secretion”; i.e., their stomachs continue to secrete a copious quantity of acid juice after they have emptied.<sup>4</sup> Although the volume of the secretion may be reduced by a relatively large dose of atropine, the secretion is not abolished as is the normal continuous secretion.<sup>4a</sup> This suggests that in such patients some abnormal process is concerned, or that some process which plays a minor role in the normal state has been activated. It is possible that histamine is being produced excessively by an irritated mucosa, since the secretory response to the ordinary doses of histamine used is not prevented by ordinary doses of atropine<sup>5</sup> (for atropine action, *vide infra*).

The nature of the stimuli which give rise to the continuous secretion of gastric juice is uncertain. The solution of the problem awaits a complete knowledge of the factors concerned in the secretory response of the stomach to a meal.

*Period II. The Period of Digestive Secretion.*—This is the secretion that occurs in response to a meal. For clarity and simplicity, *this period is divided into three phases*, the cephalic, the gastric, and the intestinal.<sup>6</sup> Each phase is named to denote the region in which the stimuli are acting to cause secretion. This assists in the analysis of the subject.

**PHASE 1. THE CEPHALIC PHASE.** This phase denotes that the stimuli are acting in the region of the head.

The stimuli are the sight, smell, taste, and thought<sup>7</sup> of food and act in the presence of appetite through (A) *conditional reflexes* (the

*Secretagogues* are naturally present in meat juice and certain other foods. Their presence can be demonstrated by perfusing meat juice through a pouch of the entire stomach with the vagi sectioned (Fig. 1). By this means any substance can be tested for "gastric secretagogues." We never use more than 50 c.c. of an aqueous solution of the substance in order to avoid stimulation by distention. For example, if the stomach is distended with 150 to 300 c.c. of water, it will secrete, but not if 50 c.c. of water is continually perfused through the stomach. A solution of egg white perfused through the stomach does not stimulate; but if the egg white is digested with HCl-pepsin, and then perfused, stimulation occurs. If the perfusion is continued for one-half hour, as in our tests for secretagogues, the stomach secretes during that period and continues to secrete above the control level for 1.5 hours and sometimes longer. Alcohol, 2 to 7 per cent, and histamine, 10 to 25 mg. in 50 c.c. of water, perfused through the stomach stimulates the secretion of acid.

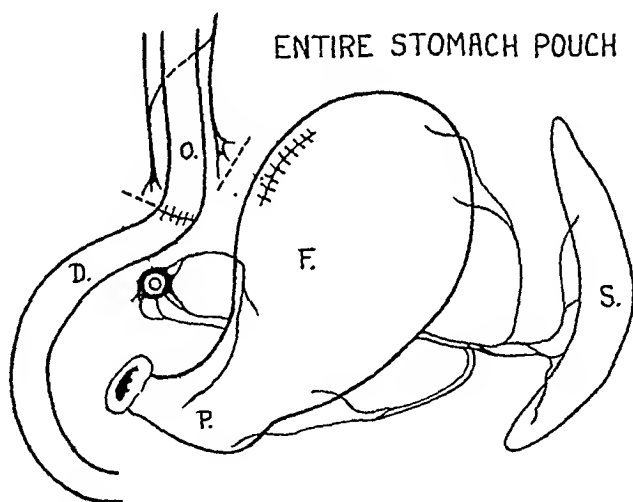


FIG. 1.—A pouch of the entire stomach. All the vagus branches are sectioned, with the possible exception of one that leaves the right vagus and passes to the celiac ganglion. However, such a pouch does not manifest a "psychic secretion." Secretion of such a pouch can be inhibited via the splanchnic nerves, there is no evidence that stimulation of acid production can occur via the splanchnic nerves. Distention of the pouch and perfusion with meat and liver extract and other solutions containing secretagogues stimulates acid production.

PHASE 3. THE INTESTINAL PHASE. This phase denotes that the stimuli are acting in the intestine.

(A) *Secretagogues*, or chemical substances, are the only type of stimuli which stimulate gastric secretion on application to the intestine.

Mild distention has no effect. Undue distention or irritation of the intestine at first inhibits gastric secretion, I believe, reflexly. If injury to the mucosa is produced, stimulation may result from the absorption of secretagogues, possibly histamine, produced locally.

various branches of the vagi have been sectioned, and to which compensatory changes occur after vagotomy. *It should be remembered that vagotomy causes other changes than an annulment of the cephalic phase of gastric secretion.* Since vagotomy should decrease the total secretion of acid to a meal, it should have a favorable effect in preventing postoperative jejunal ulcer. However, vagotomy would have no effect on a secretion due to the production of histamine by an irritated gastric or intestinal mucosa, the likelihood of the occurrence of which would be diminished as the result of a decrease in the total production of acid in response to a meal. The section of the vagi decreases the tone of the gastric musculature at least temporarily, and retards permanently the rate at which solid or thick pasty foods are evacuated from the stomach. (a) This might tend to increase the gastric phase of secretion. (b) In addition, the vagotomy would prevent "acid inhibition" of the gastric phase from the intestine from occurring, at least to a large extent, and these two factors, (a) and (b), may compensate for the abolition of the cephalic phase and negate the advantage gained by the vagotomy. Further, if the vagi contain vasodilator nerves which oppose the vasoconstrictor nerves in the splanchnics, then vagotomy might favor a decrease in the blood supply of the gastric and intestinal mucosa. Thus, the physiologist is not surprised that the procedure of vagotomy in operations for ulcer is mooted. It is one of those biologic questions in which so many positive and negative factors may be concerned that the answer cannot be predicted. The question can only be answered by the study of clinical results and by the effect of vagotomy in animals that develop ulcer, such as Mann-Williamson dogs (gastrojejuno-stomy with the alkaline digestive juices diverted to the ileum).

**PHASE 2. THE GASTRIC PHASE.** This denotes that the stimuli are acting in the stomach.

Two types of stimulating agents applied to the stomach excite the parietal cells to secrete. They are: (A) *mechanical distention* and (B) *secretagogues*, or chemical substances of which there are two types: (1) those which are *naturally present in food*, e.g., lean meat, liver, and milk whey; and (2) those which *arise from the digestion of food*, such as split-protein products and possibly fatty acids.

*Mechanical distention* is the only adequate type of mechanical stimulus known. Rubbing the mucosa with a glass rod, a feather, or sand does not stimulate the secretion of acid.<sup>3</sup> Beaumont observed secretion in response to distention, as did Pavlov. Pavlov attributed it to a "psychic" response; the dog thought food was being placed into his stomach. But Pavlov did not cut the vagi to ascertain whether his interpretation was correct. Distention of the stomach with the vagi sectioned stimulates gastric secretion and hence the secretion cannot be "psychic" in origin (Fig. 1).

A partial obstruction of the pylorus should increase gastric secretion by prolonging the gastric phase. Whether such actually occurs will depend on the extent to which the obstruction excites mechanisms which inhibit secretion, such as reflex inhibition via the splanchnics or vagi, acid inhibition from acid in the stomach, and gastritis. The results of controlled experiments show that partial pyloric obstruction increases gastric secretion in some animals.<sup>17</sup> It should, and usually does, increase the average acidity of the gastric contents (hypernormal acidity), because of the partial retention in the stomach of the acid secreted.

*Resection of the pyloric portion of the stomach*, although the pyloric mucosa does not secrete acid and pepsin, decreases the gastric phase of secretion.<sup>18, 19, 19a</sup> The pyloric portion of the stomach normally contributes to the gastric phase by increasing the effectiveness of secretagogues and distention (*vide infra*).<sup>19</sup> When the pyloric portion is excised, the remainder of the stomach secretes less acid when a secretagogue solution is applied. With the pyloric portion excised and the vagi sectioned above the diaphragm, very little secretion occurs when secretagogues are applied.<sup>20</sup> Thus, section of the vagi would abolish the cephalic phase and excision of the pyloric portion of the stomach would reduce the gastric phase. In such a stomach the secretion of acid in response to a meal would result chiefly from food acting in the intestine, or the intestinal phase; the amount of secretion should be markedly reduced unless the gastric remnant undergoes hypertrophy and hyperplasia, or the jejunal mucosa becomes irritated and produces histamine. If such a stomach empties rapidly, then much of the gastric juice formed from the intestinal phase would be buffered and neutralized only by the pancreatic juice, and bile and succus entericus. (An enteroenterostomy of the ascending and descending loops of jejunum, or an *en Y* or Roux operation by shunting the bile and pancreatic juice away from the gastroenterostomy predisposes to jejunal ulcer.)

*Gastroenterostomy* should affect only the gastric phase, provided it facilitates gastric evacuation. If the jejunum is overdistended by the food, then some reflex inhibition of secretion should occur. When performed for adequate reasons, it gives relief because (a) it tends to provide more "rest" to the ulcerated area, (b) the additional gastric orifice tends to diminish intragastric tension, (c) the average acidity of the contents tends to be diminished. The acidity of the gastric contents is diminished as a result (a) of improved gastric evacuation which decreases the gastric phase, (b) of improved enterogastric regurgitation, and (c) probably of secretory inhibitory reflexes from the jejunum. The operation fails chiefly because the jejunum is more sensitive to acid irritation than the duodenum and the gastric secretory mechanisms of the patient are too sensitive or "keyed at a high level," so the buffering and neutralizing action of the alkaline juices is not adequate to offset the susceptibility of the jejunal mucosa. The operation apparently yields better results in middle-aged and older patients,

Secretagogues which act in the stomach also act in the intestine. Numerous other substances<sup>3, 12</sup> applied to the intestine stimulate gastric secretion; for example, soaps, fatty acids, and peptone. Whether soaps are normally present in sufficient concentration to stimulate is conjectural. Neutral fat in the intestine inhibits gastric secretion (enterogastrome production). According to Shay and his associates,<sup>13</sup> sodium oleate (15 per cent) or soap depresses gastric secretion, which depression, as in the case of that due to olive oil and 40 per cent glucose, disappears after from 1.5 to 2.5 hours; then the secretion returns to normal or may go above the normal, as is also observed after suppression of secretion with atropine. This action of fat is one reason why, after the patient with ulcer has received milk and cream on the hour during the day, it is frequently necessary to do a "therapeutic aspiration" of the stomach at 11:00 P.M. to 2:00 A.M. That is, after the inhibition due to fat is over, the gastric secretion returns to a high rate. Another reason is that the administered alkali is absorbed as such and as NaCl along with water, and augments secretion as when Ringer's or Locke's solution is given by clysis. A possibility that should receive some consideration in explaining the stimulation of gastric secretion by alkalies is that the alkali in the intestine counteracts the "acid inhibition" of gastric secretion from the intestine (*vide infra*); this is entirely conjectural.

*What Amount of Juice Is Produced as a Result of the Stimuli Acting in Each Phase?*—A definite answer to this question cannot be given. Estimates are given in Table I. *Dog*: Those for the dog are fairly reliable and are based chiefly on my own observations. *Man*: Those for man on the continuous and cephalic secretion are based on my observations. Those for the gastric phase represent a guess. Those for the intestinal phase are based on Garbat's observations on duodenal feeding in ulcer patients. They may be abnormal.

*A Consideration of Some Abnormal Conditions.*—In the note under Table I, it is pointed out that operations in the upper abdomen are likely to cause a "hypercontinuous secretion." This we have observed many times. For example, after making a Pavlov pouch, the pouch may "hypersecrete" for a few days up to two weeks. It may occur after making a pouch of the entire stomach, especially if saline solution is given.<sup>14</sup> It is shown especially after total enterectomy in dogs, and it is most likely to occur when Ringer's or Locke's solution is given by clysis.<sup>15</sup> Some have seen it after converting a Pavlov pouch into a Heidenhain pouch, which sections the vagal innervation of the pouch, and have called it a "paralytic secretion."<sup>16</sup> Several years ago, we<sup>16</sup> demonstrated how a "peptic ulcer" would enlarge after exposing it for photography, unless the postoperative hypersecretion was buffered by frequent feedings. This "hypercontinuous" secretion does not always occur; however, atropine definitely decreases, but does not abolish it.<sup>12</sup>



administration of fatty chyle, soap, and properly emulsified fat does not. A highly purified extract of duodenal mucosa has been prepared which inhibits gastric secretion and motility when injected parenterally.<sup>23</sup> In man the inhibition caused by the introduction of 40 c.c. of olive oil into the duodenum lasts for from 1.5 to 2.5 hours.<sup>13</sup>

*Acid Inhibition.*—This expression is used to indicate that the presence of acid (0.2 to 0.4 per cent) in the stomach or intestine inhibits gastric secretion. Whether or not acid inhibition occurs depends on the nature and potency of the secretory stimulus. Thus, inhibition by acid is not observed under all conditions. Acid (0.36 per cent) in the stomach inhibits the action of secretagogues in the stomach (intra-gastric chemical phase), but not that of secretagogues in the intestine. Acid in the intestine inhibits the action of secretagogues in the stomach and in the intestine. When the secretory stimulus is strong, then acid in the intestine is less likely to inhibit, if at all. For example, when secretagogues are acting in the stomach and intestine simultaneously, acid in the intestine does not definitely inhibit. When gastric secretion is excited by histamine, acid in the intestine does not inhibit. The cephalic phase of gastric secretion is refractory to the inhibitory action of acid in the stomach or duodenum.<sup>24, 25</sup>

In view of the foregoing qualifications of acid inhibition of gastric secretion reported by Wilhelmj's<sup>26</sup> and Babkin's<sup>25</sup> laboratories, it is not surprising that the literature on acid inhibition is apparently contradictory. Some have observed it in man and others have not.<sup>27-31</sup> In the dog we<sup>6, 12</sup> found the effect of the introduction of acid into the duodenum to be uncertain.<sup>31</sup> To complicate the picture further, the continuous perfusion of acid (0.36 per cent) through a Thiry fistula of the duodenum and jejunum will usually after a latent period of about forty-five minutes cause a stimulation of gastric secretion.<sup>12</sup> This stimulation occurs after the mucosa has been injured with the acid. The feeding of a meal after such an experiment sometimes results in a hypernormal secretory response of a Pavlov pouch. Repeated daily perfusion of the Thiry fistula with acid for a period may cause a hypernormal continuous secretion.<sup>12</sup> It is possible that irritation of the intestinal mucosa with acid or any other agent releases histamine, or a histamine-like substance, as does irritation of the skin. This has to be considered in the interpretation of the secondary rise of gastric secretion when substances, such as 15 per cent sodium oleate, etc., are introduced into the intestine of man.<sup>13</sup>

Summarizing, a primary inhibition of gastric secretion from the intestine may occur as the result of enterogastrone liberation, reflex inhibition, or in the case of injury, the absorption of nonspecific inhibitory substances. A subsequent return of gastric secretion may be the result of escape of the stomach from inhibition due to the neutralization or disappearance of the inhibitory stimulating agent, or in the pres-

particularly in the presence of some pyloric stenosis due to an old ulcer, than in younger patients, probably because of the declining gastric secretion due to age and the atrophic changes in the gastric mucosa associated with prolonged stenosis. The operation of pyloric occlusion with gastroenterostomy, which was designed to be applied to the younger group of patients and to simulate the anatomic condition of pyloric stenosis in the middle-aged, considered inadequately the physiologic factors concerned in gastric secretion, the regulation of gastric acidity and the susceptibility of the jejunal mucosa to acid-pepsin irritation. (A pyloric stump that cannot drain well is subject to mechanical factors which may cause distress.)

The important role that the alkaline juices play in the presence of a gastrojejunostomy is demonstrated by the Mann-Williamson dog, which develops a jejunal ulcer in almost 100 per cent of cases. In this operation the alkaline juices, except the locally produced succus entericus, are diverted to the lower ileum, so the acid chyme irritates the jejunal mucosa. The gastric acidity curve in response to a meal does not show the normal terminal decrease <sup>16, 21, 22</sup> and the stomach continues to secrete for a longer period than normally. The gastric phase of secretion is probably increased due to the increased emptying time and in some animals the intestinal phase appears to be definitely prolonged. The volume of secretion is reduced, but not abolished by atropine, which suggests that the irritated mucosa is producing histamine.<sup>5</sup>

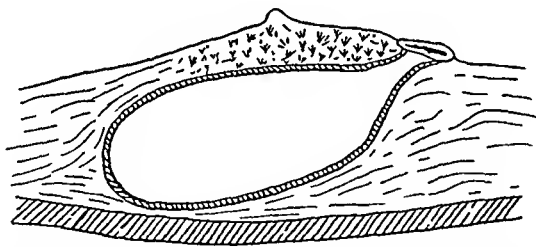


Fig. 2.—An autotransplant of the acid-secreting portion of the stomach made by the pedicle graft method. The pouch secretes when the animal is fed a meal. This is the crucial proof of the existence of a humoral mechanism for gastric secretion.

#### INHIBITION OF GASTRIC SECRETION

Nervous and humoral mechanisms are concerned in the inhibition of gastric secretion. *Nerves:* The splanchnic nerves and the vagi contain inhibitory fibers for gastric secretion, so mental states may inhibit secretion. Distention of the intestine inhibits secretion probably reflexly.

*Enterogastrone.*—Fat or concentrated sugar solution (10 per cent or above) introduced into the intestine inhibits gastric secretion. That the inhibition caused by fat is due to a chalone referred to as enterogastrone is clearly established. For example, the introduction of olive oil or cream into the intestine of a dog with an autotransplanted pouch (Fig. 2) inhibits the secretion of the pouch; whereas, the intravenous

*Does a Humoral Mechanism for Gastric Secretion Exist?*—This question can be stated more simply as follows: When we eat a meal, does some agent enter the blood and cause the gastric glands to secrete?

This question can be answered affirmatively. When a meal not containing too much fat is fed, an autotransplanted pouch secretes (Fig. 2). This shows that a humoral mechanism is in part concerned in the gastric secretory response to a meal.<sup>35</sup> This observation also provides us with a method by which we can ascertain how various stimulating agents applied to the stomach or intestine stimulate gastric secretion.

The fact that an autotransplanted pouch secretes tells us nothing regarding the nature of the humoral agent.

*What Is the Nature of the Humoral Agent?*—The humoral agent (a) may be histamine; (b) may be a gastrin or a hormone different from histamine, or histamine-like; (c) may be secretagogues absorbed from the food in the stomach and intestine.

We have sought to answer this question by biochemical and physiologic methods. We first started out to identify the principle or the gastrin in acid extracts of pyloric mucosa.

A. ISOLATION OF HISTAMINE FROM ACID EXTRACTS OF PYLORIC MUCOSA.—Edkins and others showed that the subcutaneous injection of acid extracts of pyloric mucosa would stimulate gastric secretion. He called the active principle gastrin. He proposed a theory which maintained that the contact of food and acid with the pyloric mucosa caused a hormone, gastrin, to be formed, which was carried by the blood to the parietal cells. It was soon shown that a gastrin was present in extracts of fundic mucosa and of numerous other tissues. Since those tissue extracts which stimulated gastric secretion also depressed blood pressure like histamine, many believed that Edkins' gastrin was histamine, or a histamine-like substance.

Following the lead of Luckhardt, Koch, and Keeton, we undertook to isolate and identify the active principle. We<sup>35</sup> made the following observations. Acid extracts of the pyloric mucosa contain a substance which stimulates gastric secretion when given subcutaneously or intramuscularly. These extracts given intravenously rapidly depress blood pressure like histamine. The activity of the extracts is destroyed by histaminase. Histamine was isolated from such extracts as a crystalline sulfate and picrate. The secretory and vasodepressor activities, expressed as a ratio, found in the original extract, remained relatively constant in all fractions including the final step of crystallization. *This evidence showed that Edkins' gastrin is histamine.* However, the evidence does not warrant the conclusion that histamine is the gastric hormone. All that can be deduced is: either histamine is the gastric hormone, or there is no gastric hormone, or the true gastric hormone has not been extracted from gastric mucosa.

McIntosh<sup>36</sup> has studied the amount of histamine in the blood before and after feeding. He could not find a significant increase in blood

ence of irritation it may be due to the production of a histamine-like substance, which may give rise to a hypernormal response to a meal or to a hypercontinuous secretion.

#### THEORETICAL OUTLINE AND EVIDENCE REGARDING HOW PARIETAL CELLS MAY BE STIMULATED TO SECRETE BY VARIOUS STIMULI

The older literature on this subject has been reviewed by Babkin<sup>3a, 31, 32</sup> and by me.<sup>33</sup> Since then some progress has been made. The newer evidence will be presented with the pertinent older evidence in outline form with an attempt to distinguish between the known and unknown features of the problem.

1. *Extrinsic nerves*, as for example the secretory nerves in the vagi. The nerve impulses conducted by these nerves (a) may exert a direct secretory influence on the cell by releasing at their nerve endings acetyl choline or histamine, or by depolarization associated with the action potential which is associated with the "nerve impulse"; (b) may stimulate by causing vasodilation or a favorable vascular reaction for secretion; (c) may cause the production of a specific hormone, or a gastrin.

"Sham feeding," it is well known, does not cause a Heidenhain pouch (a pouch devoid of vagal innervation) to secrete. Hence, if the vagal secretory nerves stimulate the parietal cells by releasing a substance as postulated in *b* and *c* above, the substance acts only locally and does not pass into the circulation. Of the various possibilities, the local release of acetyl choline is most probable according to existing information.

2. *Mechanical distention*, as in the gastric phase. Mechanical distention may stimulate (a) by causing vasodilation and increased motility directly or through intrinsic nerves; (b) by stimulating intrinsic secretory nerves which release acetyl choline or histamine or excite the cells by the action potential; (c) by direct mechanical stimulation; (d) by producing a specific hormone, gastrin; or (e) by releasing histamine as the result of mechanical stimulation, since rubbing the skin may cause vasodilation by the *alleged* production of a histamine-like substance.

Evidence will be presented later which indicates that mechanical stimulation acts only locally. That is, mechanical stimulation of the main stomach does not cause a transplanted pouch to secrete.

3. *Secretagogues or chemical substances*, as in the gastric and intestinal phases. Secretagogues may stimulate (a) by being absorbed into the blood; (b) by producing a hormone, gastrin; (c) by stimulating intrinsic secretory nerves, as in mechanical distention; (d) or, as in the case of the stomach, by direct chemical contact with the parietal cell through local absorption or diffusion; (e) or, by causing vasodilation.

Evidence regarding how secretagogues act will be given later.

A hypothetical analysis such as this has to be made before a problem can be attacked experimentally. Such an analysis is frequently incomplete because of a deficiency in existing knowledge.

This evidence, it may be argued, indicates the existence of a hormone mechanism for gastric secretion. Since secretagogues applied to the intestine or stomach cause a transplanted gastric pouch to secrete, secretory nerves are ruled out. Since 100 mg. of the liver extract applied to the stomach stimulated secretion and 400 mg. intravenously were required to stimulate, it is obvious that the 100 mg. applied to the stomach did not stimulate by being absorbed into the blood. Hence, it may be deduced that secretagogues applied to the stomach stimulate a transplanted pouch by causing the elaboration of a hormone. Such a deduction cannot be unequivocally accepted. The crucial experiment would be to use a dog with both a transplanted pouch and a pouch of the entire stomach, and then to apply to the latter an amount of "purified" secretagogues that would stimulate the transplant but would not stimulate the transplant when given slowly intravenously (*vide infra*).

### TWO POUCH DOG

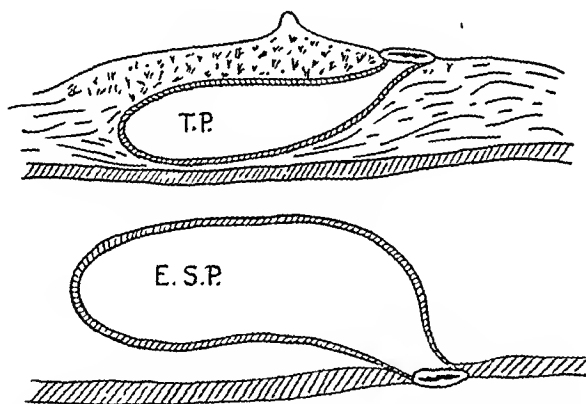


Fig. 4.—Analysis of the action of secretagogues when applied to the gastric mucosa. When liver extract is applied to the main pouch (E.S.P.), the transplanted pouch (T.P.) secretes.

*Site of Origin of the Humoral Agent.*—It is clear that a humoral mechanism for gastric secretion exists, because on feeding a dog with a transplanted pouch, the transplant secretes. This does not tell us whether the humoral agent comes from the stomach, or from the intestine.

The only way this question can be answered is to use a dog with a pouch of the entire stomach and with an autotransplanted pouch, or a "two-pouch" dog (Fig. 4). Then it would be possible to stimulate the stomach or the intestine and ascertain whether the transplant secretes. Secretion by the pouch can only be due to a humoral agent. (These studies<sup>19</sup> were made recently in our laboratory by Dr. R. A. Gregory.) The observations to date may be summarized as follows: (1) A humoral mechanism is *involved* in the action of *secretagogues* in the stomach. Perfusion of the entire stomach pouch (Fig. 4) causes the transplant

histamine after feeding. Neither did he find a significant increase in blood histamine after injecting 1 mg. subcutaneously. Thus, the parietal cells are more sensitive to histamine than the method for measuring the histamine in the blood. Histamine could be the humoral agent, because when it is injected very slowly intravenously it stimulates gastric secretion without causing vasodilation or a fall in blood pressure.<sup>37</sup> Since atropine (1 mg.) during the period of its maximum effect abolishes the secretory response to a meal in the dog, it is necessary to conclude that if histamine is a normal humoral agent atropine must prevent it from being formed.<sup>37a</sup>

B. CAN SECRETAGOGUES ON BEING ABSORBED INTO THE BLOOD BE THE HUMORAL AGENT?—Not being able to ascertain whether histamine is the humoral agent, we decided to ascertain whether secretagogues on entering the blood might be the humoral agent.

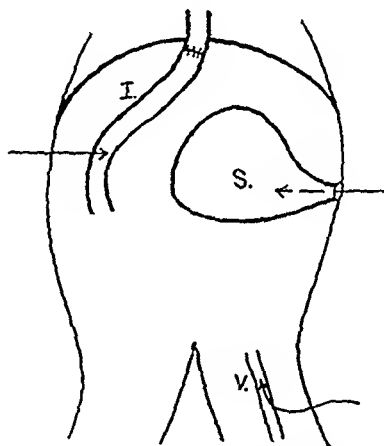


Fig. 3.—Analysis of stimulation of gastric secretion by secretagogues; 100 mg. of secretagogues applied to the stomach. *S.* caused secretion; whereas, 100 mg. intravenously (*V.*) was required. Liver extract introduced into the intestine (*I.*) caused the pouch to secrete.

We<sup>38</sup> found that Lilly's preparation (No. 343) of the antipernicious anemia fraction of liver contained about 70 per cent of the secretagogues in liver. We freed this extract of vasodepressor material and injected it slowly intravenously. Gastric secretion was stimulated. This showed that secretagogues could stimulate if they should be absorbed as such from the intestine and stomach. We could not prove by chemical methods that secretagogues were absorbed from the stomach and intestine.

However, we made a "purified" preparation of secretagogues from liver extract and found that 400 mg. of this extract were required to stimulate when injected intravenously and only 100 mg. were required when applied to the stomach (Fig. 3). This result, which has been recently confirmed,<sup>39</sup> shows that secretagogues applied to the gastric mucosa are more potent than secretagogues injected intravenously.

effect of local procaine anesthesia on the elicitation of the humoral mechanism was studied.<sup>19</sup>

A 5 per cent solution (50 c.c.) of procaine was perfused through the main stomach for fifteen to thirty minutes and then distention or secretagogue was applied. Procaine was also applied to the transplant, it having been found that procaine (25 c.c. of 5 per cent solution) injected subcutaneously had no effect on gastric secretion. Some of the results are shown in Table II. The results may be summarized as fol-

TABLE II

SECRETION OF TRANSPLANT GASTRIC POUCH ON PERFUSION OF POUCH OF ENTIRE STOMACH FOR 0.5 HR.\*

PROCEDURE†	NO. OF EXPER- MENTS	MAIN POUCH‡			TRANSPLANT‡		
		VOL., 1.5 HR.	FA MG. HCl	TA MG. HCl	VOL., 1.5 HR.	FA MG. HCl	TA MG. HCl
Perfusion M. St. with L. E., with No procaine	22	9.3	9.2	36.2	2.0	2.0	3.0
Procaine to M. St.	12	3.5	0	12.7	1.3	0	0.7
Procaine to Tr.	10	5.5	4.7	24.6	1.9	1.6	2.3
Meal, mixed	4	22.8	17.6	32.9	6.9	2.8	6.3
Liver extract, 8 gm. No. 343	2	12.3	6.4	14.6	4.3	1.8	3.7
Meal (Procaine M. St.)	3	19.8	19.6	26.5	5.0	2.7	3.7
Liver extract M. St.	2	14.3	16.3	23.7	4.4	1.8	3.3
Distention (M. St.)	10	11.4	13.9	22.2	2.0	0	0.9
Distention + procaine	6	5.8	0	7.1	1.4	0	1.1
Perfusion 25 mg. histamine	6	6.4	42	55	2.4	3.2	5.7
Perfusion + procaine	3	7.1	29	41	3.3	5.6	7.4
Perfusion 2% alcohol	4	9.3	21	36	3.0	5.3	6.0
Perfusion + procaine	5	11.5	38	50	4.3	5.5	8.2

\*Procaine 50 c.c. of 5 per cent solution for 15 to 30 minutes; 25 c.c. of 5 per cent procaine subcutaneously has no effect on response of pouch to perfusion.

†L. E. Liver extracts. M. St. Main stomach. Tr. Transplant.

‡The pouches were secreting no free acid when the experiments were performed.

lows: (1) Procaine applied to the pouch of the entire stomach abolishes the response to distention and secretagogues. (2) Procaine applied to the pouch of the entire stomach prevents the transplant from secreting in response to secretagogues applied to the former. (3) The procainized transplant secretes when secretagogues are applied to the entire stomach pouch or to the intestine, or when a meal is fed. (4) Procaine applied to the entire stomach pouch does not prevent stimulation of both pouches on the application of histamine (10 to 25 mg. in 50 c.c. of water) or alcohol (50 c.c. of 2 to 7 per cent) to the pouch of the entire stomach.

Indirect evidence strongly indicates that alcohol stimulates gastric secretion by causing the liberation of histamine.<sup>41</sup> If histamine is the gastric hormone, then alcohol acts on a different point in the gastric secretory mechanism than secretagogues.

The procaine evidence shows: (a) that procaine does not act on the parietal cells (see 3 above); (b) that procaine probably does not act by preventing the absorption of secretagogues, since it is practically devoid of vascular action; (c) and that procaine most likely acts by block-

to secrete (4 dogs, numerous experiments). (2) A humoral mechanism is *involved* in the action of *secretagogues* in the intestine. On feeding the animal, which has an esophagoduodenal anastomosis (Fig. 5), the transplant secretes (4 dogs, numerous experiment). Application of liver extract to a Thiry fistula of the intestine (Fig. 5) causes the transplant to secrete (1 dog, 7 experiments). (3) A humoral mechanism is *not involved* in the action of mechanical distention. Distention of the main stomach (Fig. 5) does *not* cause the transplant to secrete (4 dogs, numerous experiments). (4) Distention of the transplant usually causes secretion.

Thus, the mechanism for mechanical and secretagogue stimulation of gastric secretion is not the same. Also, if a humoral agent is involved, it does not come from the parietal cell, because in both cases the parietal cells of the entire stomach pouch secrete.

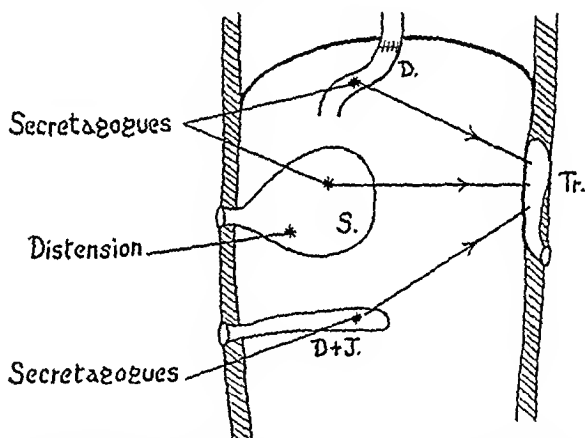


Fig. 5.—Secretagogues placed in the duodenum (*D*), the stomach (*S*). A Thiry fistula of the duodenum and jejunum (*D + J*) causes the transplant (*Tr.*) to secrete. Removal of the pyloric portion of the stomach (*S*) reduces the response to secretagogues and to distention. Distention of stomach (*S*) does not cause the transplant to secrete.

*Site of Origin in the Stomach of the Humoral Agent Produced by Secretagogues.*—A pouch of the "entire stomach" from which the pyloric portion of the stomach has been removed does not secrete as much acid in response to secretagogues as when the pyloric portion is intact.

To ascertain whether the pyloric portion of the stomach contributes to the humoral mechanism, we resected the pyloric antrum from a two-pouch dog (Fig. 4). After the resection of the antrum, application of secretagogues to the remainder of the stomach caused the transplant to secrete. However, less secretion was obtained than before antrectomy. Thus, the pyloric mucosa contributes to, but is not the sole origin of, the humoral mechanism obtained from the stomach.

*Analysis of Local Stimulating Mechanism in the Stomach as Revealed by Use of Local Procaine Anesthesia.*—Since the mechanism for the stimulation of secretion by distention and secretagogues is different, the



effect of local procaine anesthesia on the elicitation of the humoral mechanism was studied.<sup>19</sup>

A 5 per cent solution (50 c.c.) of procaine was perfused through the main stomach for fifteen to thirty minutes and then distention or secretagogue was applied. Procaine was also applied to the transplant, it having been found that procaine (25 c.c. of 5 per cent solution) injected subcutaneously had no effect on gastric secretion. Some of the results are shown in Table II. The results may be summarized as fol-

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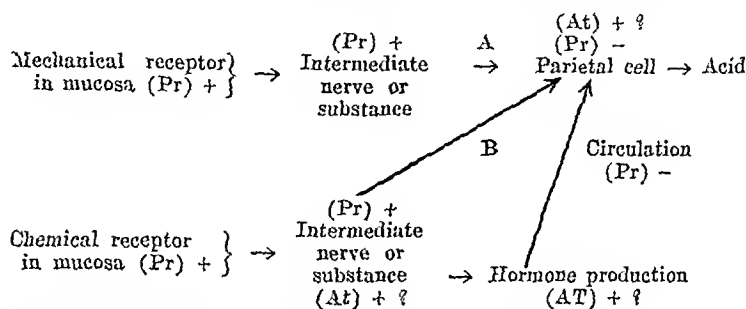
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ing a local receptor mechanism (mechanical and chemical) which causes a local secretory response to mechanical stimulation and the liberation of a hormone on secretagogue stimulation. *Two types of receptors probably exist in the gastric mucosa: one mechanically excitable, which does not release hormone, and another chemically excitable, which releases hormone.* Alcohol probably acts directly to liberate histamine.

This concept can be illustrated by the following diagram:



*A* and *B* could involve either a secretory or a vasomotor reflex.

Atropine and procaine do not prevent histamine and alcohol stimulation, because histamine is absorbed and alcohol causes, by direct action, histamine formation.

Atropine prevents the action of secretagogues (liver extract) injected intravenously. It reduces, but does not prevent, the action of moderate amounts (0.5 mg.) of histamine, but in small amounts (0.2 to 0.3 mg.) does prevent histamine stimulation.

(*At*) + ? Atropine inhibits in adequate doses but the site of action is questionable

### *Evidence Required to Settle Definitely Nature of Humoral Agent.—*

1. To show that histamine is the hormone, some method more sensitive than those available will be required; or we will need to find some agent that will destroy histamine rapidly, and will at the same time stop a transplant from secreting. Histaminase acts slowly; it does not prevent injected histamine from acting; it does not reduce the gastric secretory response to a meal.

2. To rule out definitely the possibility that secretagogues act by being absorbed into the blood, it must be shown, for example, that 100 mg. of secretagogues applied to the stomach will stimulate a transplant, and that the same quantity intravenously will not. Or

3. To find some agent which will stimulate secretion in a transplant when applied to the entire stomach pouch, but which will not stimulate the transplant when given intravenously. Fatty acids and soaps are alleged to stimulate secretion when applied to the stomach but not when injected intravenously. But Gregory<sup>19</sup> found that soap confined to the stomach does not stimulate secretion.

4. To find some agent in the blood that stimulates, but is not a protein-split product resulting from absorption.

5. (A) One should probably search further for a gastrin that is not histamine. (B) One should isolate and identify the secretagogue or secretagogues in liver and meat extract.

*Effect of Atropine.*—In the dog the effect of atropine is well established. One milligram subcutaneously abolishes the normal continuous secretion and the gastric secretory response to a meal for from one to three hours. It abolishes all the phases of gastric secretion. The same dose produces a definite but limited inhibition of the response to histamine; the inhibition consists chiefly of a decreased volume output of acid without much change in acidity;<sup>37a</sup> the acidity may increase slightly.

The exact site of action of atropine is uncertain. It undoubtedly acts to block the action of secretory nerves. If histamine acts only on the parietal cells, then atropine probably acts also in part on the parietal cell.<sup>42</sup> Atropine does not abolish the secretory response to alcohol.<sup>41</sup> This indicates that alcohol releases histamine,<sup>40</sup> and, if histamine is a normal humoral agent, that alcohol releases histamine by a different mechanism (irritation) from that concerned in the release of histamine by secretagogues in food. This observation is of much interest in that it demonstrates the existence of a mechanism for gastric secretion that cannot be blocked by atropine. This would indicate that in man when a secretion is occurring that cannot be blocked for an hour or more by atropine histamine or a histamine-like substance is responsible.

In man atropine (1 or 2 mg.) abolished the *normal* continuous secretion but not that seen in some patients with duodenal ulcer. Its effect on the response to a meal is contradictory.<sup>43</sup> This is not surprising in view of the fact that in most studies patients with ulcers were used and the methods, stimulating agents, and dose of atropine and other factors are varied. (This subject deserves investigation in the light of recent knowledge.) Atropine decreases the volume output of acid in response to histamine,<sup>45</sup> and to alcohol, as in the dog.<sup>4a</sup> In patients with ulcers on hourly milk and cream diet atropine apparently only decreases the volume output of secretion<sup>44</sup> as in the dog with a jejunal ulcer;<sup>5</sup> it certainly does not abolish it as a rule. These observations constitute strong presumptive evidence that in patients with ulcer histamine or a histamine-like substance is produced. If those reported failures of atropine, in doses adequate to cause complete xerostomia and disturbances of vision, to abolish the gastric secretory response to a meal in man are not due to the presence of an ulcer or a "preulcer" condition, then normal men have a gastric secretory mechanism not found in the normal dog. Then man's predisposition to ulcer may be due to this tendency to produce histamine or a mechanism not readily blocked with atropine.

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## THE MANAGEMENT OF GASTRIC RESECTION FOR THE "POOR RISK" PATIENT

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AT TIMES the surgeon attends a patient urgently in need of surgical treatment for chronic disease of the stomach, but in poor or even critical physical condition. Starvation, old age with cardiorenal and vascular changes, gastric retention with edema and atony of the wall, and infection of the gastric contents are some of the factors involved singly or in combination to make the patient a poor risk for difficult or prolonged operation on the stomach and for the postoperative complications that may arise. We have found certain measures recently employed in the handling of these poor risk patients to be especially worth while.

A period of hospitalization before operation is essential. This may occupy from six to fourteen days and occasionally a longer time is necessary. There has never been occasion to regret this delay in surgical treatment and usually we have been rewarded by improvement in the patient's general condition. Ample opportunity is provided for the establishment of proper water, protein, and electrolytic balance. When gastric retention is complete or almost so, this balance must be accomplished chiefly by the parenteral route. The administration of Ringer's solution replaces salts, and fluid in the form of glucose solution is also readily given. Records of the intake and output of fluid and frequent determinations of the blood chlorides are essential. The production of edema is carefully avoided. Transfusions of blood help to replenish low blood proteins and to aid in the restoration of lowered hemoglobin and erythrocyte levels. Plasma transfusions are also given when the blood proteins are low. Vitamins B and C are injected parenterally if not taken by mouth. During this period digitalization of the patient may be accomplished if cardiac decompensation is present. An attempt is made to ascertain the presence of renal insufficiency and to correct it if possible before operation.

Careful preparation of the stomach is important. When the gastric residue is large or obstruction of the stomach is complete and of long standing, the gastric content is almost always infected and the walls of the stomach are thickened, atonic, and edematous. Contamination of the operative field with the contents of such a stomach would invite sepsis, and suturing the walls would encourage disaster from leakage. The infection can be considerably reduced, the edema diminished, and

the muscular tonus at least partly revived by proper preparation. Complete obstruction of the stomach requires lavage through a large stomach tube with a considerable amount of fluid in order to remove the larger particles that may be in the residue. Repetition at least once may be necessary. Often bits of undigested food and undissolved medicinal tablets are removed in this manner. A small nasal tube is then passed into the stomach and connected to the continuous suction apparatus. The patient maintains a continuous lavage by drinking clear fluids at frequent intervals, and this treatment is supplemented by periodic lavage carried out by the nursing or intern staff. Tap water is generally employed. The tube is clamped off and disconnected several times a day so that the patient may be up and about the ward or room. Having the patient out of bed for several periods during each day is an important part of his routine which should be maintained whenever possible. At meal times he is given a clear fluid diet, dilute meat broths, sweetened fluids, tea and jello (milk and unstrained orange juice will later obstruct the small tube and should not be given). The tube is clamped off during the meal and for the ensuing hour or two. This allows even the patient with obstruction to absorb some nutrition and gives him the satisfaction of taking something at meal time. Later, suction and lavage are resumed. In a few days the stomach becomes grossly clean and tends to return to a more normal size. The edema of the wall subsides and opportunity is afforded for it to regain some of its lost tonus. On the last day or two preceding operation, dilute hydrochloric acid in water may be given by mouth or used in the lavage for its supposed bacteriostatic action.

Objections to this rather strenuous "cleaning up" process might be raised on the ground that bleeding might be incited in the diseased stomach. In our experience this has not occurred whether the obstruction is caused by carcinoma or by ulcer. In the patients without obstruction, particularly those in whom severe hemorrhage has occurred, the regime described above is not fully carried out. It is not necessary if there is little or no residue in the stomach. Even for the unobstructed patients, however, the clear fluid diet is enforced for at least three or four days prior to operation, and lavage of the stomach is carried out for about forty-eight hours with the small indwelling tube and suction apparatus as described above. Dilute hydrochloric acid in tap water is given if gastric acidity is low, but it is omitted for patients with ulcer who have high acid readings. In all cases the last lavage is given on the evening before operation, but the suction is continued until the patient is called to the operating room. The nasal tube is left in the stomach during the operation and is allowed to drain by gravity or is attached to a suction device.

The choice of preoperative medication for the poor risk patient is of considerable importance. Large doses of sedative are avoided. Usually a dose of  $\frac{1}{8}$  or  $\frac{1}{16}$  gr. of morphine is given before the patient

goes to the operating room, and to this may be added  $\frac{1}{200}$  gr. of scopolamine. In some of the elderly patients, a small dose of sodium phenobarbital may be given hypodermically instead of the morphine. A dose of sodium phenobarbital on the evening prior to operation will help insure a night of rest.

In these bad risk patients, partial or subtotal gastrectomy is performed entirely under local anesthesia. When this type of anesthetic is skillfully administered, it is possible to carry through a difficult and prolonged operative procedure with the deliberate precision necessary for the successful execution of the Halsted silk technique. In fact, the local anesthesia and the use of silk supplement each other in accomplishing the procedure, for the gentle handling of tissue helps to make the use of local anesthesia possible in gastric resection, and the use of local anesthesia makes possible the prolonged operating time necessary for carrying out the details of the Halsted method. Both factors are of considerable importance in bringing the debilitated patient successfully through gastric resection.

The use of local anesthesia for upper abdominal laparotomy and gastric resection has been described previously. Credit for the anterior splanchnic block is given to Braun, but Finsterer did much to further its recognition as an acceptable method of anesthesia in operations on the stomach. Recently Ogilvie, Allen, and Rienhoff have advocated its use. Paek, Devine, and others have also mentioned it.

Employment of local anesthesia in connection with the use of silk for gastric resection in poor risk patients appears to justify its description here in some detail. It is probably true that, even in the best hands, local anesthesia for some reason or other may fail to be satisfactory for this sort of operative work. In most cases, however, skill, thoroughness, and accuracy employed in the administration of the anesthetic solution will be rewarded by successful anesthesia. Novocain is usually employed in dilutions of 0.75 or 1 per cent and to each ounce 2 or 3 drops of adrenalin solution are added. Field block of the abdominal wall is preferable to direct infiltration. The skin is carefully prepared with soap, water, alcohol, ether, and tincture of merthiolate solution, and is suitably draped. The field is outlined with intracutaneous wheals beginning at the tip of the ensiform process and extending down the costal margins to points just lateral to the rectus sheath on either side. From these points the series of wheals is continued vertically downward along the lateral borders of the rectus sheaths on either side to points at or slightly below the level of the umbilicus. The two series of wheals are joined by extending them to or immediately below the umbilicus. Employing a somewhat longer needle, introduced through these wheals, the fascia is pierced at intervals of about 1 cm. for the entire circumference of the field and a few cubic centimeters of novocain solution is injected at each point of perforation. The injection is carried out with a hand syringe and the plunger

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ments are divided close to the stomach and, generally speaking, a high partial or subtotal gastric resection is done. If the benignancy of the lesion is doubtful, it is managed as though it were malignant. In high resections it is occasionally necessary to use additional novocain solution to infiltrate the lesser omentum near the cardia of the stomach. Particular care must be taken not to perforate a vessel in this region because hematomas form very rapidly and are difficult to control. If the duodenum must be mobilized, it is sometimes necessary to inject novocain solution just to the right of the duodenal attachment before beginning the incision in the posterior parietal peritonum. The duodenum is divided between clamps with the electroscalpel. The fat is carefully removed from the proposed site of inversion, the duodenal stump is turned in with a Parker-Kerr inverting suture of treated gastrointestinal catgut (small caliber) and is further turned in with interrupted mattress sutures of fine silk placed with straight cambric needles or with very fine French-eyed needles. The silk sutures are placed about  $\frac{1}{8}$  inch apart and are tied just tightly enough to appose the tissues firmly without cutting or producing strangulation. These are further protected by neighboring omental tabs. Further division of the attachments along the greater and lesser curvatures by the method described above is continued until the level selected for division of the fundus is reached. The fat is removed from the greater and lesser curvatures at this site. The nasal tube is withdrawn by an attendant until its tip can be felt in the fundus above the proposed site of amputation. As a rule clamps are not employed in the amputation of the fundus; we prefer to depend upon the thorough preparation of the stomach, careful walling off of the operative field with suitable packs, and the use of suction in the open viscus to prevent contamination. In practice these methods have proved very satisfactory in the prevention of sepsis and the advantage of obtaining direct hemostasis in the open stomach is evident.

Infiltration of the base of the transverse mesocolon from within the lesser peritoneal cavity renders its manipulation painless, in case the splanchnic block has worn off or has not included this area. An incision is made in the transverse mesocolon through an avascular area near its base and to the left of the middle colic vessels. A loop of small intestine just distal to Treitz' ligament is brought through the opening in the transverse mesocolon to make the retrocolic anastomosis. Usually the retrocolic Reichel-Polya type of repair is used following gastric resection. In the very high resections in which the mesocolon cannot be sutured to the gastric stump, Treitz' ligament is divided (as described by Lahey) by extending the incision in the transverse mesocolon downward. This permits the exit of only the descending loop of jejunum through the opening in the transverse mesocolon which is later closed around the single descending loop of jejunum. Before dividing the fundus of the stomach, the loop of jejunum that has been

is carefully withdrawn before each injection in order to be certain that none of the solution enters a blood vessel. The tissues should not be flooded with excessive amounts of novocain solution. When the field block has been completed, the incision is developed. Recently we have come to prefer the midline epigastric incision in most of these cases, though the right or left muscle-splitting or the paramedian incision is used if, for any particular reason, one of them appears to be indicated. As soon as the peritoneum is exposed, it is infiltrated with novocain solution over a fair-sized area and incised in one place. Further incision of the peritoneum is preceded by injection with novocain solution, which is carried back for a distance of about 3 or 4 inches on either side of the incision. Small retractors are then inserted. Exposure is gained with the utmost care and gentleness.

At this point an attempt may be made to decide by inspection whether the lesion is operable, or whether further manipulation is necessary before resectability can be determined. Before any considerable intra-abdominal manipulation is carried out, the splanchnic region is infiltrated with novocain, following essentially the method of Braun. A needle is inserted into the retroperitoneal space below the left lobe of the liver, to the right of the abdominal aorta, at or about the level of the celiac axis. The needle is inserted until it is felt to impinge upon the body of the first lumbar vertebra and then is withdrawn slightly. From 40 to 75 c.c. of the novocain-adrenalin solution is introduced slowly with due care to prevent intravascular injection. Operability is then confirmed by palpation which is facilitated by an exploration into the lesser sac if necessary. All intra-abdominal manipulations must be carried out with great care and the softest possible touch. No pain should be inflicted upon the patient at any time as it will cause him to strain, contracting the musculature of the abdominal wall and pushing the intra-abdominal viscera out into the operative field. Such a catastrophe demands the supplemental use of general anesthesia. It can be prevented in almost every case by the accurate placement of the local anesthetic and by care and gentleness in operative manipulations. Extensive subtotal gastrectomies have been done entirely under local anesthesia in this manner, but total gastrectomy has required the use of general anesthesia.

Silk (Halsted technique) has been used for several years in this clinic for general surgical work. It has proved to be admirably adapted to gastric surgery and particularly to these cases of gastric resection done under local anesthesia. The essential steps of the present method as applied to gastric resection are: The attachments along the greater and lesser curvatures are divided by sharp dissection, the vessels being clamped with fine pointed hemostats before division and immediately tied with fine silk ligatures. In malignant disease, the lesser and greater omenta are widely excised, together with the greater part of the stomach. If resection is indicated for a benign ulcer, the omental attach-

ments are divided close to the stomach and, generally speaking, a high partial or subtotal gastric resection is done. If the benignancy of the lesion is doubtful, it is managed as though it were malignant. In high resections it is occasionally necessary to use additional novocain solution to infiltrate the lesser omentum near the cardia of the stomach. Particular care must be taken not to perforate a vessel in this region because hematomas form very rapidly and are difficult to control. If the duodenum must be mobilized, it is sometimes necessary to inject novocain solution just to the right of the duodenal attachment before beginning the incision in the posterior parietal peritonum. The duodenum is divided between clamps with the electroscalpel. The fat is carefully removed from the proposed site of inversion, the duodenal stump is turned in with a Parker-Kerr inverting suture of treated gastrointestinal catgut (small caliber) and is further turned in with interrupted mattress sutures of fine silk placed with straight cambric needles or with very fine French-eyed needles. The silk sutures are placed about  $\frac{1}{8}$  inch apart and are tied just tightly enough to appose the tissues firmly without cutting or producing strangulation. These are further protected by neighboring omental tabs. Further division of the attachments along the greater and lesser curvatures by the method described above is continued until the level selected for division of the fundus is reached. The fat is removed from the greater and lesser curvatures at this site. The nasal tube is withdrawn by an attendant until its tip can be felt in the fundus above the proposed site of amputation. As a rule clamps are not employed in the amputation of the fundus; we prefer to depend upon the thorough preparation of the stomach, careful walling off of the operative field with suitable packs, and the use of suction in the open viscus to prevent contamination. In practice these methods have proved very satisfactory in the prevention of sepsis and the advantage of obtaining direct hemostasis in the open stomach is evident.

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brought through the opening in the transverse mesocolon is sutured to the posterior wall of the stomach, above the proposed line of division, with interrupted sutures of fine silk placed about  $\frac{1}{8}$  inch apart with fine cambrie needles. The distal end of the jejunal loop is at the greater curvature and the proximal loop at the lesser curvature of the stomach. It is important that the sutures be placed accurately and that the submucosa be included in each stitch (as described by Halsted). The sutures must be tied with care so that the parts are firmly apposed but are not cut or strangulated. Continuous sutures of silk are never used. When the posterior line of silk sutures has been placed and tied, incisions are made with the electroscalpel down to the submucosa in the anterior and posterior walls of the stomach, at the proposed site of amputation. This brings the vessels into view and the larger ones are ligated with fine silk ties passed on cambrie needles while the smaller vessels can be safely coagulated with the electroscalpel. A small opening is then made into the lumen of the stomach and all fluid is aspirated by suction. The stomach is amputated by completing the incisions with the electroscalpel through the mucosa on all sides, and the specimen of the stomach containing the lesion is removed from the operative field. When this is done carefully, there is no spilling of gastric content. In addition, the field is always blocked off with drapes to prevent accidental contamination. An incision with the electroscalpel is made in the loop of jejunum parallel to the opening in the stomach and hemostasis and prevention of soiling are carried out as described in the technique of opening the wall of the stomach. A second posterior line of sutures, consisting of a continuous gastrointestinal catgut hemostatic suture, is placed through all the layers of the posterior aspect of the gastrojejunal stoma and is completed anteriorly as a Connell type of suture. The anterior line of sutures is completed by the introduction of Halsted mattress sutures of fine silk passed on fine cambrie needles and is further reinforced with interrupted sutures of the same material, thus completing the anastomosis. All laparotomy pads are removed from the operative field and the gloves of the surgeon and all assistants are changed. Fresh towels are draped about the field and the abdominal wound and peritoneum are reinfiltrated with local anesthetic. The opening in the transverse mesocolon is then sutured with interrupted sutures of fine silk, around the gastric stump, or it is closed and fixed around the descending loop of the jejunum if the amputation has been very high and division of Treitz' ligament has been carried out. Final inspection for hemostasis and the security of closure of the duodenal stump is made before the closure of the abdominal wound is begun. The laparotomy wound may be closed in layers with interrupted silk sutures or with heavy dermal retention sutures placed about 2 cm. apart through all layers. The wound is dressed with gauze and adhesive strapping applied in such a manner that it will not interfere with movements of the lower thorax in deep respiration.

When performed in the manner described, gastric resection often requires from four to five hours, and in very difficult cases as long as six hours has been needed. In this length of time it is usually necessary to reanesthetize the splanchnic area and the abdominal wall, and this should be done as soon as the patient complains of the slightest discomfort. Aside from a transient drop in blood pressure which may occur if the local anesthetic is introduced rapidly in large quantities, the general condition of the patient usually remains essentially unaltered throughout the procedure. If the patient becomes restless at the end of three or four hours, a small dose of morphine or of sodium luminal may be repeated. It is gratifying to see the "bad risk" patient appear so well at the end of the long operation and to realize that the utmost has been accomplished to relieve him with the least risk to his precarious hold on life. It is a great satisfaction also to know that the intra-abdominal operative work has been deliberately and thoroughly done.

The patient is returned to his bed in the semi-Fowler position, but is moved frequently (at least every two hours). Inhalations of carbon dioxide-oxygen are given at intervals to promote deep respirations. Patients in their late sixties and seventies are assisted to sit on the edge of the bed twice daily beginning the first postoperative day, and on several occasions these elderly patients have been allowed to sit in a chair at the bedside for a short period each day, very soon after operation.

The nasal tube is connected to the suction device as soon as the patient is returned to his room. Continuous gastric aspiration is maintained, usually for forty-eight hours, but irrigation is forbidden. The patient is allowed nothing by mouth for the first seventy-two hours, but is encouraged to rinse his mouth, and the nurse is required to carry out oral hygiene at frequent intervals. Fluid balance is maintained by the parenteral route for the first few days, care being taken not to overload the cardiovascular system and to avoid edema. Blood transfusion is done if the patient does not appear to be progressing favorably, but it is not always required. An enema is ordered on the morning of the third day after operation. On the third day 1 ounce of water is given by mouth every two hours. On the fourth day this is increased to 2 ounces every two hours, alternating water with albumin water. On the fifth day, when progress is favorable, clear fluids (tea, broth, coffee, jello) are given in amounts up to 3 ounces not oftener than every three hours. No milk or fruit juice is given. On the morning of the sixth day a coddled egg is added and that evening a small baked potato is allowed. Beginning on the seventh postoperative day, the diet is very gradually increased by adding thin gruels and other bland foods. It must be remembered that the gastric capacity is much diminished and the feedings should be correspondingly small at first.

TABLE I  
TABULATION OF CASES

CASE NO.	AGE YR.	CONDITION	PERIOD OF PREPARATION	LESION	OPERATION	OPERATIVE COURSE	CONVALESCENCE
1	74	Weak, fat, flabby, auricular fibrillation	1 wk.	Carcinoma of antrum of stomach	Gastric resection, distal three-fourths of stomach; Reichel-Polya repair, 4 hr. 10 min.	Pulse 64 to 112; B.P. 106/80, 96/64, 100/70; pressure dropped slightly during administration of spinal anesthetic	Uneventful; highest temperature 99.8° F.
2	51	Starved, emaciated, weak; loss of 49 lb. in 11 wk.	10 days	Carcinoma of stomach with complete pyloric obstruction	Gastric resection, distal three-fourths of stomach; Reichel-Polya repair, 4 hr. 15 min.	Pulse 72 to 108; B.P. 110/70 to 150/90	Uneventful; highest temperature 101° F. on day of operation; afebrile thereafter
3	49	Intractable pain from 2 wk. ulcer, 18 mo.; starvation, dehydration, emaciation, weakness	from 2 wk.	Large benign gastric ulcer; lesser curvature of stomach	Gastric resection, distal four-fifths of stomach; Reichel-Polya repair, 4 hr. 5 min.	Pulse 50 to 70; B.P. 96/70 to 130/70	Transfusion reaction; temperature 103° F., third postoperative day, then uneventful
4	57	Gastrointestinal bleeding, pyloric obstruction; vomiting, dehydration, weakness	1 wk.	Prepyloric carcinoma; ulcer, complete obstruction	Gastric resection, distal three-fourths of stomach; Reichel-Polya repair, 4 hr. 30 min.	Pulse 76 to 100; B.P. 122/74 to 140/74	Uneventful; highest temperature 101° F. day of operation; afebrile thereafter

5	74	Weak, anemic, scule; 1 wk. vomiting for 6 wk.	Carcinoma of gastric antrum, fixation and obstruction; 20% gastric residue at 6 hr.	Gastric resection, distal three-fourths of stomach; Billroth II repair, 4 hr. 45 min.	Pulse 52 to 80; B.P. 130/70, 74/44, 126/70; pressure dropped sharply during administration of splanchnic anesthetic	Temperature to 101.8° until fourth postoperative day, then afebrile; obstruction at gastroenterostomy stoma, tenth to seventeenth postoperative day; uneventful thereafter
6	48	Gastroenterostomy 7 yr. previously; anorexia, pain, diarrhea, loss of 40 lb. 2 yr. before entry	Large carcinoma of the stomach, great or curvature above stoma of gastroenterostomy	Gastric resection, five-sixths fundus; resection and anastomosis of jejunum; Reichel-Polya repair, 5 hr. 55 min.	Pulse 80 to 112; B.P. 106/60, 90/60, 110/70; pressure dropped slightly during administration of splanchnic anesthetic	Signs of atelectasis and fever to 101.6° F. on fifth and sixth postoperative days; afebrile thereafter
7	52	Duodenal ulcer 15 yr.; gastroenterostomy 10 yr., without benefit; severe pain 1½ mo.; emaciated, very weak	Jejunal ulceration near gastroenterostomy site	Resection, end-to-end anastomosis, resection distal three-fourths of fundus of stomach; Reichel-Polya repair, 6 hr. 10 min.	Pulse 120 at start; 80 to 100 during operation; B.P. 112/86, 80/60, 106/60; pressure dropped during administration of splanchnic anesthetic	Atelectasis and pneumonia; died seventh postoperative day
8	63	Massive gastric hemorrhage, pyloric obstruction, anemic, hemoglobin 20%	Penetrating duodenal ulcer with pyloric obstruction and hemorrhage	Resection, three-fourths fundus of stomach; Reichel-Polya repair, 5 hr. 55 min.	Pulse 72 to 88; B.P. 102/70, 90/70, 110/80; pressure dropped slightly during administration of splanchnic anesthetic	Atelectasis first postoperative day; temperature 103.8° F., gradually subsided; uneventful after fifth day

TABLE I—Cont'd

CASE NO.	AGE YR.	CONDITION	PERIOD OF PREPARATION	LESION	OPERATION	OPERATIVE COURSE	CONVALESCENCE
9	75	Epigastric pain 1 yr.; 15 days weak, senile, anemic, hemoglobin 34%; loss of 15 lb.		Annular constricting lesion, antrum of stomach; one large metastatic nodule in lesser omentum; 10% gastric residue, 6 hr.	Resection, distal four-fifths of stomach; Reichel-Polya re-pair, 3 hr. 40 min.	Pulse 60 to 100; B.P. 110/60 to 130/80	Uneventful; highest temperature 100° F., rectally
10	66	Indigestion, epigastric pain, loss of 15 lb. in 4 mo.; thin, emaciated, anemic	10 days	Annular constricting ulcerative carcinoma in antrum of stomach, complete obstruction	Resection, five-sixths of stomach; Polya-Balfour anastomosis, 4 hr. 35 min.	Pulse 60 to 90; B.P. 110/60, 90/50, 120/60; pressure dropped slightly during administration of splanchnic anesthetic	Temperature 100.6° F. rectally second postoperative day; afebrile thereafter
11	39	Penetrating duodenal ulcer with hemorrhage, intractable pain, rheumatic heart disease, mitral stenosis and insufficiency; cardiac decompensation on several occasions in past	10 days	Duodenal ulcer penetrating into pancreas, with hemorrhage	Gastric resection, distal three-fourths of stomach including duodenal ulcer; Reichel-Polya re-pair, 4 hr. 50 min.	Pulse 90 to 110; B.P. 90/64, 76/50, 120/70; pressure low at start, dropped slightly after anesthetic given; rose toward end of operation	Pulmonary atelectasis third postoperative day; temperature 103.4° F.; uneventful after that episode



12	60	Epigastric pain, vom. 12 days iting, 5 mo.; loss of 30 lb.; starved, emaciated, dehy- drated, anemic	Prepyloric ulcerative, constricting car- cinoma with ob- struction	Resection, distal three-fourths of stomach; large ul- cer crater extended into the head of pancreas; Reichel- Polya repair, 4 hr. 30 min.	Pulse 70 to 100; B.P. 112/68 to 130/75	Satisfactory 5 days; temperature to 102° rectally sixth day; peritonitis de- veloped eighth day; patient died ninth postoperative day; autopsy: acute hemorrhagic pan- creatitis with peri- tonitis; no gastro- intestinal leakage
13	53	Penetrating duodenal 6 wk. ulcer, complete py- loric obstruction, hemorrhage, severe pain; several large hemorrhages under medical regime; emaciated, weak, very anemic	Large duodenal ulcer penetrating into the pancreas; com- plete obstruction and hemorrhage	Devine exclusion op- eration; resection, three-fourths stomach; Reichel- Polya repair, 4 hr. 5 min.	Pulse 120 at start; later 72 to 84; B.P. 130/70, 70/50, 100/64; pressure dropped during sec- ond splanchnic in- filtration	Unventful; highest temperature 99.4° F., rectally; afebrile
14	72	Starved, anemic, de- 5 wk. hydrated, emaci- ated, delirious (peliagra), com- plete gastric ob- struction	Benign ulcer, gastric antrum, penetra- tion into pancreas; obstruction	Resection, distal four- fifths of stomach; Reichel-Polya re- pair, 6 hr. 15 min.	Pulse 60 to 112 dur- ing most of opera- tion; last hour, 120; B.P. 150/84; 70/50 for short time following in- jection of splanchnic area; 140/70 at end of operation	Unventful except for infection of abdom- inal wound with rise of temperature to 102° F.

It is important not to depress these patients by sedation in the post-operative period. When the operative work has been done carefully and with little trauma the patient usually has very little discomfort after his operation and  $\frac{1}{2}$  gr. of codeine at required intervals ordinarily is enough to keep him comfortable. If not, a single small dose of sodium phenobarbital will probably not depress him too much and will help to insure rest. Morphine is rarely required and seldom given to these patients after operation.

We usually leave the sutures in place for from fourteen to sixteen days in these feeble patients. It has also been found desirable to keep them in the hospital for several days longer than the younger or stronger patients.

On the University of California Service at the San Francisco Hospital, during the past year, we have had fourteen patients whom we considered to be "poor risks." The tabulation of cases appended (Table I) shows in brief the type of patient to whom our regime has been applied and the immediate result accomplished. These cases were selected because operation upon the stomach was essential. All patients were especially prepared and were operated upon entirely under local anesthesia. In each case three-quarters or more of the stomach was resected.

#### SUMMARY

Certain measures employed in the management of patients with gastric lesions previously considered inoperable because of the poor condition of these patients have increased the number of operations successfully performed. Chief among these are:

1. A period of hospitalization before operation for preparation which includes the treatment of hypoproteinemia, the correction of fluid and electrolyte balance, the administration of vitamins, the treatment of cardiac decompensation, and the detection and correction of renal insufficiency wherever possible.

2. Thorough mechanical cleansing and decompression of the stomach by means of gastric lavage and aspiration.

3. The use of local anesthesia and silk technique. The method as applied in the performance of gastric resection in the "poor risk" case is described. Accuracy and thoroughness in the placement of the anesthetic agent and gentleness, deliberation, and care in the operative manipulations are necessary for the accomplishment of gastrectomy under these conditions.

4. Careful supervision of the postoperative care of "poor risk" patients. Such details include provision for pulmonary ventilation, frequent changes in the patient's position, the regulation of the intake of fluids, feeding, and the limitation of narcosis.

## HEMANGIOMA OF THE STOMACH

### REVIEW OF THE LITERATURE AND REPORT OF TWO CASES

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BECAUSE of the very small number of hemangiomas of the stomach recorded in the literature, two additional cases seemed worth reporting, especially in view of the fact that one of them had been the subject of a preoperative gastroscopic examination, a procedure apparently never before performed in the previously recorded cases. A review of the literature indicated the rarity of gastric hemangioma not only as compared with the frequency of hemangioma in other tissues, but also as compared with the incidence of other types of benign tumors of the stomach.

Hemangiomas are common, most are benign, and most occur on the body surface. A small number involve the viscera; and yet a smaller number involve the bone, muscle, and central nervous system. Geschickter<sup>5</sup> reported 570 instances of hemangioma from the Johns Hopkins Hospital: 370 peripheral, 135 visceral, and 65 of bone, muscle, and the central nervous system. The majority of the visceral hemangiomas, 109 or 81 per cent, involved the liver. The remaining 19 per cent involved the heart valves and other internal organs including the mesentery, kidney, and gastrointestinal tract. None of these tumors, however, involved the stomach.<sup>6</sup>

Benign tumors of the stomach, which are much less frequent than malignant growths of the organ, include adenomas, polyps, adenomyomas, leiomyomas, fibromas, lipomas, neurofibromas, dermoid and echinococcus cysts, embryonic rests of the pancreas, osteomas, and hemangiomas. In Eiselsberg's Clinic<sup>2</sup> only 5 benign tumors were found among 1,125 gastric neoplasms, an incidence of 0.44 per cent. Eusterman and Senty<sup>4</sup> estimated from cases at the Mayo Clinic that only 1.3 per cent of all tumors of the stomach treated surgically are benign. Hillstrom,<sup>3</sup> reviewing records of the Department of Pathology of the University of Minnesota, found about 5 per cent of all tumors removed at operation or discovered at necropsy were benign. Stewart,<sup>22</sup> in 11,000 post-mortem examinations, found benign tumors of the stomach in 15 per cent. Rigler and Erickson<sup>18</sup> found benign tumors in 26 per cent of

all gastric neoplasms at necropsy. In 1925 Eliason and Wright<sup>3</sup> collected 560 previously reported cases of benign tumors of the stomach and added 50 of their own, making a total of 610 cases. In 1932 Lockwood<sup>12</sup> recorded 4.5 per cent of gastric neoplasms benign, and stated that about 1,000 cases of benign gastric tumors had been reported. Since then many more have been recorded. Thus the incidence of benign tumor of the stomach has been reported variously from 0.44 per cent to 26 per cent of all gastric neoplasms. The number found at operation is much smaller than at necropsy, and few give rise to many symptoms.

The first recorded case of hemangioma of the stomach was reported by Lammers<sup>10</sup> in 1893. Since then cases have been reported by Stockis,<sup>23</sup> Guisez,<sup>7</sup> Burty,<sup>1</sup> Sherril and Graves,<sup>20</sup> Lemon,<sup>11</sup> Konjetzny,<sup>9</sup> Eusterman and Senty,<sup>4</sup> Moore,<sup>14, 15</sup> Siebner,<sup>21</sup> and Minnes and Geschickter.<sup>13</sup> In 1920 Lemon collected the first 5 cases from the literature and added 1. In 1925 Eliason and Wright collected a total of 10 from the literature in citing 610 cases of benign tumors of the stomach. Minnes and Geschickter in 1936 gathered 961 benign tumors of the stomach from the literature, of which 15 (1.6 per cent) were hemangiomas. They add a case of their own, believing it to make a total of 16. In a careful search of the literature, taking into consideration double and triple reporting of cases, we have been able to find only 12 different cases recorded.

TABLE I  
CASES OF HEMANGIOMA OF THE STOMACH\*

CASE	AUTHOR	YEAR	DETERMINATION AT
1	Lammers	1893	Necropsy
2	Stockis	1904-5	Necropsy
3	Burty	1914	Operation
4	Sherril and Graves	1915	Operation
5	Lemon	1920	Operation
6	Konjetzny	1921	Not stated
7	Eusterman and Senty	1922	Operation
8	Eusterman and Senty	1922	Operation
9	Eusterman and Senty	1922	Operation
10	Moore	1924	Operation
11	Siebner	1933	Operation
12	Minnes and Geschickter	1936	Necropsy
13	Morton and Burger	1941	Operation
14	Morton and Burger	1941	Operation

\*A case reported by Guisez has been included in the tabulations of previous authors but has been excluded from our tabulation because, on reading the original report, it appears that this lesion was esophageal rather than gastric. It was visualized through the esophagoscope at the "cardia."

The pathologic characteristics of hemangioma of the stomach do not differ from those which might be expected. Hemangioma is a true neoplastic process involving vascular tissue and is believed to arise from embryonic rests of mesodermal tissue. The types encountered in the stomach appear to have been capillary and cavernous. They are usually round, soft, smooth, and with some semblance of a capsule, though some are diffuse. Some are on a pedicle, though most are interstitial.

They lie between the mucosa and serosa and are bluish black or reddish in color. To palpation they often feel "like a mass of angleworms." They occur at varying ages, ulcerate easily, and hemorrhage is a frequent symptom.

In general the symptoms are due to ulceration, hemorrhage, disturbance of gastric function, or malignant change. The case of Burty revealed sarcomatous change. They usually produce a filling defect on roentgenologic examination and are diagnosed as benign or malignant tumors. As far as can be ascertained, no previously reported case has been subjected to gastroscopic examination. In this connection, however, Schindler<sup>19</sup> said: "Benign tumors of the stomach are by no means rare. In my experience they have been found in 1.5 to 2 per cent of all the cases gastroscoped. . . . Angiomas are so rare that it will probably be a long time before one is seen gastroscopically, but they should be easily diagnosed."

#### CASE REPORTS

CASE 1.—R. C. (Hist. No. 157373), a white man, aged 36 years, was admitted to the Medical Clinic of the University of Virginia Hospital April 9, 1940. He complained of discomfort in the epigastrium of one year's duration. He had first noticed the discomfort in the early morning and usually it had been relieved by food, soda, or exercise, and had not returned during the day, if the patient had been moderately active. It had returned, however, when he had become fatigued. The discomfort had remained as a dull, gnawing, nonradiating type of mild pain throughout the year, and had not been associated with nausea, vomiting, anorexia, hematemesis, melena, or weight loss. His past and family histories were irrelevant except that a paternal uncle had had "ulcers of the stomach."

Physical examination revealed a well-developed and nourished white man who appeared to be in good health. No physical abnormalities were discovered. His abdomen seemed entirely normal. His temperature, pulse and respiratory rates, and blood pressure were within the normal range. Laboratory examinations, including various studies of the blood, urine, and gastrointestinal tract content, likewise revealed no abnormalities.

*Roentgenologic Examination.*—The gastrointestinal tract was examined roentgenologically after ingestion of a barium meal on two occasions, six days apart. Both examinations revealed an organic lesion, a ragged area on the lesser curvature of the stomach beginning at the level of the cardiac orifice and extending downward for 6.5 cm. There was also slight spasm at the pylorus, but the remainder of the stomach and duodenum appeared normal. The six- and twenty-four-hour interval examinations of the remainder of the gastrointestinal tract revealed no other abnormality. The roentgenologist believed that a malignant tumor might be present in the stomach in the region referred to in Fig. 1.

Gastroscopic examination, by Dr. Porter P. Vinson, of Richmond, Va., revealed "a polypoid mass on the lesser curvature of the stomach near the cardia, without evidence of ulceration. It was concluded that this lesion represented a localized area of polyposis."

On the basis of the roentgenologic and gastroscopic findings a tentative diagnosis, polypoid tumor of the stomach, was made and exploratory laparotomy was advised.

*Operation.*—The patient entered the University of Virginia Hospital April 18, 1940, and after four days of preoperative treatment, laparotomy was performed.

Spinal anesthesia was employed, and the abdomen was explored through an incision in the midline of the epigastrium. Exploration of the abdominal viscera revealed no abnormality, except in the case of the stomach. There were numerous large and tortuous vessels in the upper half of the stomach wall along the lesser curvature. In addition there was a good deal of telangiectasis of the surface vessels of the stomach in this region. To palpation the involved area of the stomach wall felt like



Fig 1.—Case 1. Roentgenogram of stomach after barium meal, revealing ragged area on the lesser curvature beginning at the level of the cardiac orifice and extending downward for 6.5 cm.

a mass of angleworms. The changes were characteristic of the cavernous type of hemangioma. It was not sharply circumscribed and merged into normal looking stomach toward both the pylorus and greater curvature.

The involvement was so widespread that surgical eradication of it would have necessitated practically a total gastrectomy. This did not seem justified. A biopsy, however, seemed worth while. An incision was made high up in the stomach near the lesser curvature, and the stomach examined internally. As might have been expected,

bleeding was profuse but was readily controlled. Inspection confirmed the x-ray and gastroscopic findings in that the mucosa of the stomach, in the region referred to, was full of tortuous ridges and furrows representing the vessels beneath the surface. There was no evidence of polyposis or ulceration. A small area of the stomach wall on one side of the gastric incision was excised for later microscopic study, and the incision then closed. The appendix was removed routinely, and the laparotomy wound closed.

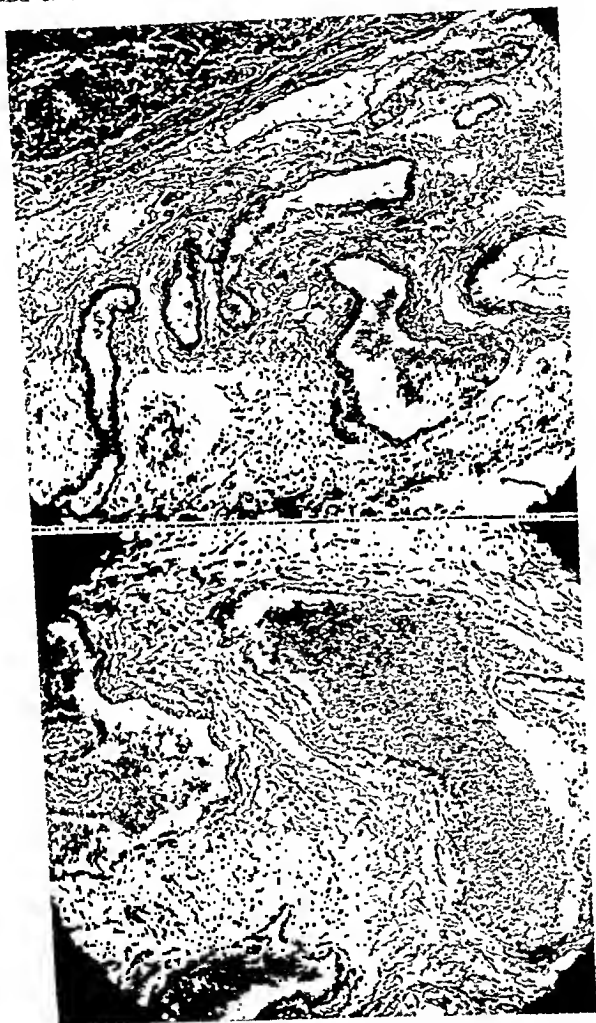


Fig. 2.—Case 1. A, many thin-walled blood vessels in the muscularis mucosae running through the submucosa (×25). B, Higher power photomicrograph of submucosa revealing thin-walled vessels in close proximity filled with blood (×60).

*Microscopic Study.*—Sections included the entire thickness of the stomach wall with a fairly thick and essentially normal mucosa. The muscularis mucosa appeared normal. The submucosa was fairly thick, and contained a large number of fairly large blood spaces with thin walls lined with endothelium. The muscularis and serosa appeared normal. The endothelial lined spaces in the submucosa seemed to

indicate the presence of a cavernous type of hemangioma. The final diagnosis was "cavernous hemangioma of the stomach."

*Course.*—The patient's convalescence was smooth and uneventful. He left the hospital on the twelfth postoperative day, tolerating a five-meal gastric diet comfortably. He has recently reported that he has no gastric symptoms, but continues to restrict his diet as directed. Should symptoms ever reappear, it is probable that radiotherapy should be considered.

CASE 2.—Unfortunately, nothing is known of the clinical features of this case except that the patient was a woman, aged 36 years, operated upon in a small hospital in a nearby town. Efforts to obtain further information have been unavailing.

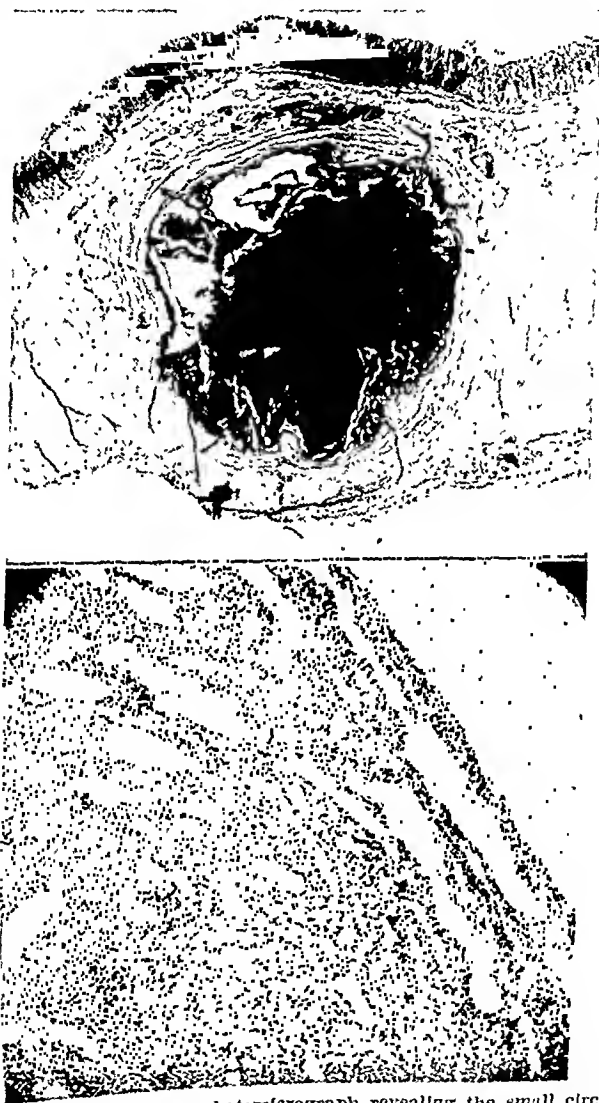


Fig. 3.—Case 2. A, Low-power photomicrograph revealing the small circumscribed angiomatous tumor entirely within the muscularis of the stomach wall ( $\times 10$ ). B, Higher power photomicrograph revealing the mass of cells with very little stroma. The open blood spaces lined by endothelium can be seen. ( $\times 25$ .)



Tissue labeled "cyst of the stomach wall" was sent for study, and received by the Department of Pathology of the University of Virginia Hospital, Nov. 11, 1939. The tissue was in formalin fixative, and appeared to be relatively fresh. No other tissue accompanied the specimen, but it is impossible to know whether the tissue represented the patient's primary disease or was removed as an incidental finding during the course of an operation for some other disease.

Macroscopically, the tissue consisted of a small area of the entire thickness of the wall of the stomach, in the center a circumscribed mass 1 cm. in diameter, apparently representing a hemangioma in the muscularis.

Microscopically, the mucosa and submucosa were normal except for numerous dilated blood channels in the submucosa. Situated within the muscularis was an area which consisted of a mass of cells with very little stroma. The cells were rounded, fairly uniform in size and shape, and contained scanty cytoplasm with fairly large reticular nuclei. Situated within the mass of cells were numerous small and large channels which were lined by a flattened layer of endothelium, and were filled with blood. There was some invasion of the intermuscular spaces by the cells, but the lesion did not extend as far as the margins of the tissue removed. The final diagnosis was "cavernous and plexiform hemangioma of the stomach with rather marked endothelial proliferation."

#### SUMMARY

A brief review of hemangiomas and other benign tumors of the stomach has been given. Hemangiomas of the stomach appear to be quite rare. After a careful search of the literature, we have found only 12 previously recorded cases.

We have recorded two additional cases of hemangioma of the stomach discovered at operation. The first, a patient with a diffuse cavernous hemangioma involving a large area of the stomach wall and responsible for mild gastric symptoms, was studied gastroscopically. Though the tumor was not diagnosed correctly at the time of the gastroscopic examination, a definite organic lesion was noted. No previously recorded case of hemangioma of the stomach appears to have been examined gastroscopically. The second case report is incomplete and, because of our inability to obtain clinical data, is based only on the gross and microscopic study of tissue removed at operation elsewhere.

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# ABSCCESS OF THE STOMACH WALL\*

## WITH REPORT OF 1 CASE

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THIS communication is the report of acute abscesses of the wall of the stomach in chronic gastritis, occurring in the absence of chronic peptic ulcer. Abscesses of the stomach wall not directly the result of a demonstrable ulcer of the mucosal surface and not part of a phlegmonous



Fig 1—Mucosal surface of stomach with granular appearance and loss of rugae at pyloric end

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gastritis must be considered a rare and unique phenomenon. Several pathologists among whom inquiries were made stated that they had never encountered it. A search of the literature failed to reveal a similar case.

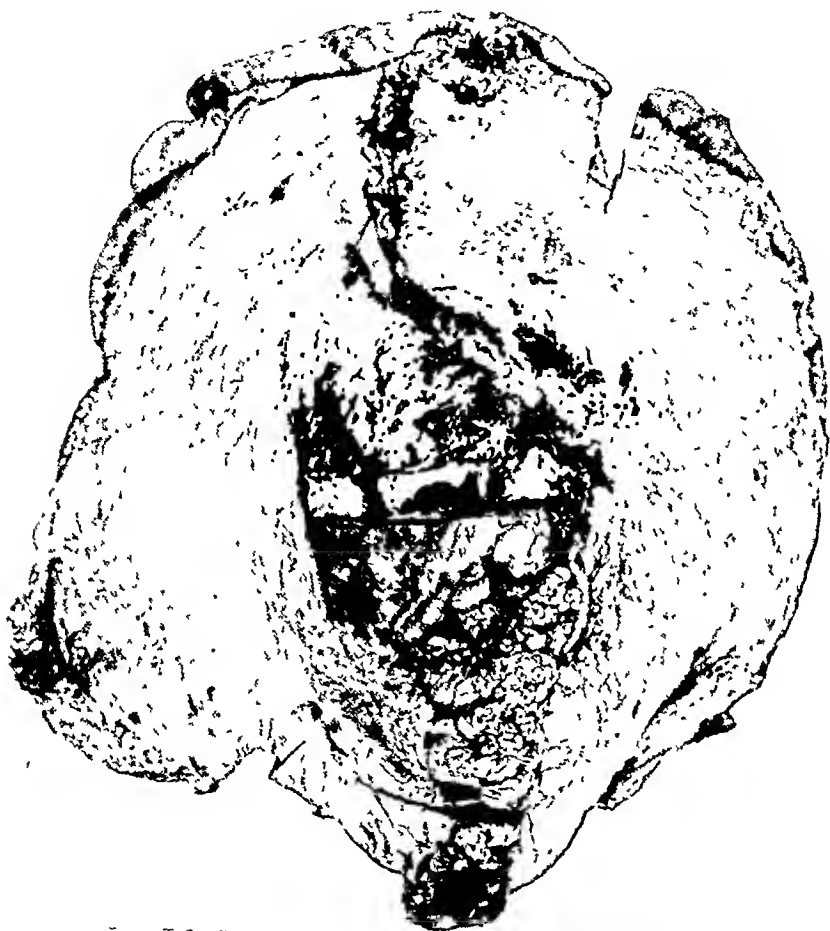


Fig. 2.—Serosal surface of stomach with abscesses

#### CASE REPORT

The patient, a male, aged 35 years, a grocery clerk, was admitted to the Medical Service at City Hospital on Feb. 14, 1940, complaining of gaseous eructations and gnawing pains after eating, beginning two months previous to admission. The pain was increased by the ingestion of food and liquids. There was no nausea, vomiting, diarrhea, melena, or weight loss.

The general physical examination was entirely negative except for a tender spot in the epigastrium. The blood count showed 1,270,000 red cells and 90 per cent hemoglobin; W.B.C., 9,300; 62 per cent polymorphonuclears; and 38 per cent lymphocytes. The urine was essentially negative.

The roentgenogram showed the stomach to be orthotonic in type. Along the lesser curvature there was an indrawn area or niche formation which indicated infiltration. The duodenum was perfectly normal throughout. At six hours there was a very definite gastric retention lying along the greater curvature. There was a moderate gastric retention at twenty-four hours. The findings indicated ulceration of the prepyloric portion of the lesser curvature, possibly malignant.

A gastroscopy by Dr. H. Yarniss was reported as follows: "At the incisura in the region of the lesser curvature, posterior wall, there is a whitish ulcerated flat mass. Near the pylorus there are two whitish nodules. The action of the pylorus is asymmetrical, the lesser curvature behind the incisura not being visualized. From the gastroscopic picture there is an ulcerating carcinoma beginning at the incisura of the lesser curvature and also at the pylorus. *Diagnosis:* Carcinoma of the pyloric antrum involving the entire lesser curvature and pylorus."



Fig. 3.—Abscess in section of stomach (low power).

On March 7 the patient was operated upon for what was thought to be an early carcinoma at the pylorus. On opening the peritoneum and examining the stomach and duodenum no evidence of carcinoma or ulcer could be found. There were no adhesions and the gall bladder was found to be normal. Further exploration, entailing an opening into the lesser omental cavity, revealed a firm mass about two inches in diameter on the posterior wall of the stomach near the lesser curvature at about the level of the reentrant angle. The character of the pathology, however, could not be definitely ascertained by either palpation or inspection. Based upon

the report of the roentgenologist and the gastroscopist it was decided that the lesion was probably an early carcinoma and a resection was indicated. Hence, a subtotal resection with a Hofmeister modification of a Polya anastomosis was done.

From an examination of the gross specimen after the operation, and even after consultation with the pathologist, the nature of the lesion could not be determined and had to be deferred until after examination of sections under the microscope.

*Pathologic Report.*—"The specimen consists of a partially resected stomach measuring 15 by 13 by 4 cm. The mucosal surface has lost its rugal markings in one half. This portion is granular in appearance and has two small areas near the pylorus somewhat redder than the surrounding portion and not definitely ulcerated. There is no evidence of depressions or scars of previous ulcers. The entire wall is greatly thickened and gelatinous in appearance. The serosa is markedly discolored and hemorrhagic. In the midportion of the serosa is a firm flat mass. Histologically, the entire wall is greatly thickened and diffusely infiltrated by lymphoid and plasma

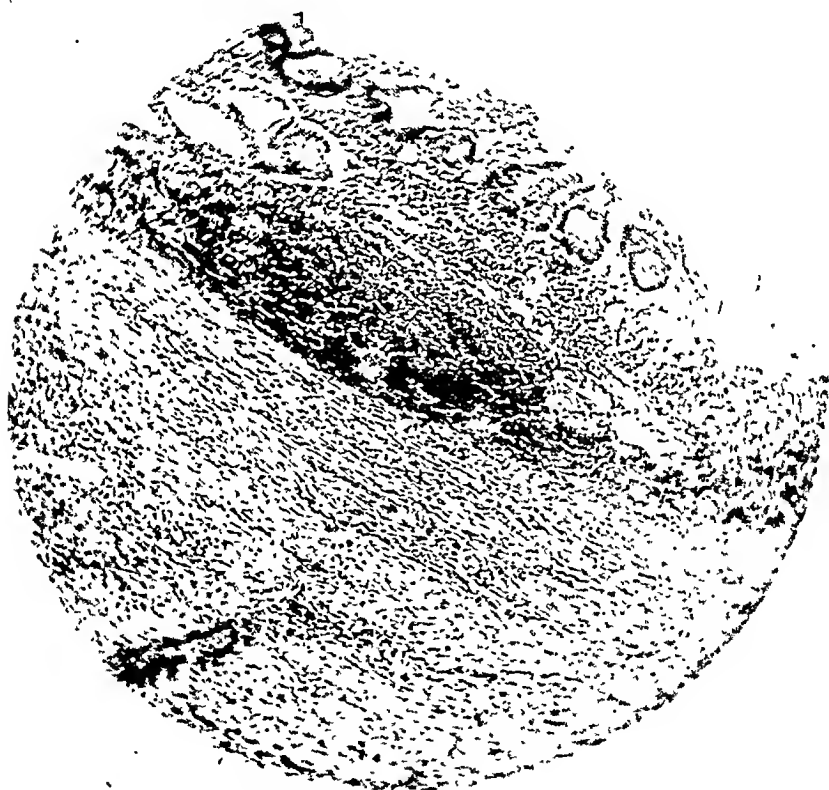


Fig. 4.—Abscesses in the subserosa (high power.)

cells. The architectural pattern of the wall is preserved and the epithelium intact except at the areas in the granular portion which, in the gross, appeared as small reddish areas. Shallow ulcers covered by a thin necrotic layer are present in this region. The surrounding portions are covered by a thin epithelium. The mass on the posterior surface consists of a group of numerous small subserous abscesses. No bacteria were demonstrated. *Diagnosis:* Chronic gastritis. Multiple acute subserous abscesses."

Although abscesses associated with phlegmonous gastritis are not uncommon, and abscesses in contiguity with gastric ulcers are occasionally seen, the character of the lesion just described seems to be unique. During the past ten years there had been only three cases of chronic gastritis at City Hospital which came to operation or autopsy. Two of these cases were seen on the operative service and one at autopsy. They differed, however, in their clinical history in that there was a characteristic history of ulcer of several months' duration in two instances, and in the third there was a history of ulcer for several years. Neither, however, showed subserous abscesses. The case found at autopsy presented a picture different from a chronic gastric ulcer, but an anemia very similar to a true pernicious anemia and nothing at all referable to the stomach. However, at autopsy there was a true phlegmonous gastritis.

The etiology of the abscess in this case is unknown. The findings, histologically, suggest that it is probably a true infectious lesion, most likely of low virulence since it caused so little disturbance in structural pattern and there is no large ulcer such as we see in other cases. Speculation might lead one to surmise that this is an early form of what later develops into a phlegmonous gastritis. If this be so, it is probably one of the earliest of this type of cases operated upon.

#### SUMMARY

1. A case of multiple subserous abscesses in a single locality of the stomach wall is described.
2. This case is considered unique as the literature is devoid of any report of a similar case.
3. The etiology remains obscure.

# ZINC PEROXIDE IN THE TREATMENT OF COMPOUND FRACTURES AND TRAUMATIC AMPUTATIONS

## A REPORT OF 18 CASES

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THERE is no unanimity of opinion about the treatment of compound fractures. Various techniques have been introduced and upheld by their proponents. However, the fundamental principles are the same. They are: (1) careful mechanical cleansing of the involved parts through débridement to remove all foreign material and devitalized tissue; (2) reduction of displacements and immobilization of the broken bones and adjacent joints and muscles; (3) administration of prophylactic antiseptics and antitetanus serums; (4) treatment of shock and excessive hemorrhage, if present.

Infection is one of the most important complications in traumatic wounds. All of these wounds are contaminated. In fact, in many wounds the contamination is so heavy that despite meticulous cleansing and the most gentle débridement, infection occurs. Furthermore, there are some types of contamination which the bodily defenses seem impotent to combat. A precise knowledge of the contaminating microorganisms present in the wound is essential. With this knowledge at hand, if hemolytic streptococci or *Staphylococcus aureus*, the gas gangrene bacilli, or other anaerobic bacteria are found, the surgeon is forewarned and, therefore, forearmed to take proper precautions against the development of infection.

This paper, first, will review some of the recent literature on the newer trends in the treatment of compound fractures; second, will present and analyze the results obtained following the use of zinc peroxide in such wounds; and third, will urge that all tissue débrided from traumatic open injuries be cultured aerobically and anaerobically.

Two methods of controlling infection in compound injuries are now receiving world-wide attention; viz., (1) the closed plaster treatment, and (2) use of the new chemotherapeutic agents. The former method consists of the immediate application of a plaster cast after the wound has been made mechanically clean by the removal of all foreign matter and by resection of all dead tissue that can be found. No antiseptic is applied. All treatment is then suspended for about a month. The proponents of this treatment claim that its success seems to depend less upon the virulence, number, and variety of bacteria present than

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\*Presently at Presbyterian Hospital, New York City.



upon the powers of resistance of living tissue toward microbial infection. When the tissues are put at rest, lymphatic drainage is minimized, and secondary contamination is prevented. As recently pointed out by Higgs,<sup>7</sup> the method has its merits as well as its disadvantages. He states that the advantages are: (1) The relief of pain and toxemia; (2) immobilization of the limb and, at the same time, mobilization of the patient; (3) the promotion of highly vascular granulations owing to which (4) necrosis and sinus formation are exceptional and, (5) bony union takes place in a minimum of time. The disadvantages are: (1) The ever present danger of development of gangrene; (2) difficulty in maintaining reduction; (3) poor functional results, especially of fractures of the femur and humerus, which are said to be extremely poor; (4) the smell; (5) the wounds remain "messy" until the plaster is discarded (septic dermatitis is common); (6) the quality of the skin growing over the fracture is poor, often ridged and thickened, and frequently raw areas are present. Furthermore, other observers<sup>23</sup> state that suppuration may spread without visible inflammatory reaction, causing pyoarthrits at some distance away from the wound. Pressure sores may be produced. The closed plaster method, Trueta<sup>24</sup> states, cannot be used in the presence of cellulitis or already established anaerobic infection.

The sulfonamide group of drugs has been used orally and as a local antiseptic to prevent infection in compound fractures. Johnson<sup>10</sup> treated 36 cases of compound fractures with sulfanilamide orally, in addition to splinting, surgery, and prophylactic antiserums. Ten of the cases (27.7 per cent) had gross infection in the wounds, 5 with *Clostridium welchii*, 5 with hemolytic streptococci on smear or culture, others with staphylococci, *Bacillus coli*, and saprophytic organisms. Three cases developed gas gangrene, and amputation was necessary in one. All recovered. A fourth case developed a serious mixed bacterial infection and recovered. On the basis of these results the drug was believed "of curative value" and recommended as a valuable adjunct to treatment. However, lower incidence of infection in compound fractures has frequently been reported in the literature without the additional use of sulfanilamide. (Hermann,<sup>6</sup> 7 per cent in 398 cases; Poyner,<sup>21</sup> 6.3 per cent in 269 cases; Reynolds,<sup>21</sup> 19 per cent in 131 cases; Ritter,<sup>25</sup> 9 per cent in 100 cases.) As regards the local use of sulfanilamide as an antiseptic, Jensen, Johnsrud, and Nelson<sup>8</sup> described a series of 39 contaminated compound fractures in which the usual toilet of the wound was followed by the implantation of powdered sulfanilamide. All the wounds were then sutured, and all healed without infection except 2. These 2 did not become infected until the fractures were recomposed several days after being closed. In a control series of 94 cases similarly treated, except for the omission of sulfanilamide, 27 per cent of the cases were infected, including 7 cases of gas gangrene. No cultures of the wounds are reported, so that we do not know with

what organisms these authors had to deal. However, the difference between the treated and control group is striking. The report of Stuck and co-workers<sup>30</sup> would appear to confirm these results, although no control series is presented.

Key, Lembeck, and Burford<sup>12, 14</sup> confirmed the results of Jensen, Johnsrud, and Nelson, and they found that the presence of the drug in the fracture site did not interfere materially with the healing either of soft tissues or of bone. Key and his collaborators<sup>13</sup> state further that "powdered sulfanilamide in a wound is similar to a test tube experiment in which a concentration of the drug of approximately 1,000 mg. is brought in contact with any bacteria which may be present in the media. In such concentrations the drug is effective against small numbers of streptococci. However, if the number of staphylococci or Welch's bacilli is relatively large, infection may occur." Campbell<sup>3</sup> reported 54 cases of compound fractures wherein sulfanilamide was used both locally and systemically. He included cases where internal fixation also was employed. Infection developed in 10 cases (19 per cent). Cultures of these revealed *Staph. aureus* in 5, Welch's bacillus in 3, and *Str. hemolyticus* in 1. In one instance the infecting organism was not recorded. No control series was presented. Campbell states, "The evidence presented does not prove definitely that sulfanilamide either is or is not a preventive of infection in compound fracture." He believes, however, that the results are sufficiently encouraging to warrant further clinical trial for evaluation under controlled conditions.\* Dunhill<sup>4</sup> and Mowlem<sup>20</sup> in referring to patients evacuated from Dunkirk believed that sulfanilamide orally in conjunction with the plaster method lessened the incidence of infection, although they admitted that reliable records were not obtainable at that time.

The sulfonamide group of drugs have not been shown to be specific against the gas gangrene organisms. The seven clinical case reports in the literature (Bohlman,<sup>1</sup> 3; Kennedy,<sup>11</sup> 1; Johnson,<sup>10</sup> 3) do not present convincing proof of the singular effectiveness of these drugs on gas gangrene. The experimental evidence is discouraging. Caldwell,<sup>2</sup> Henderson and Gorer,<sup>5</sup> Legroux,<sup>15</sup> Lockwood,<sup>18</sup> Morales-Otero and Gonzalez,<sup>18</sup> Singer,<sup>27</sup> Spray,<sup>28</sup> and Stephenson and Ross<sup>29</sup> were unsuccessful in protecting or saving experimental animals when intramuscular injections of pathogenic clostridia were given. The English authors found that a combination of sulfapyridine with specific antiserum gave some encouraging results.

Recently, however, we have had at our disposal another local antiseptic which, in conjunction with surgery, shows promise as a valuable aid in the prevention of infection. This antiseptic is zinc peroxide.

\*A recent article by Campbell and Hughes (J. A. M. A. 117: 672, 1941) gave somewhat more encouraging results, but they got 18.1 per cent infections still in 113 cases; the differences in percentage of infections between the "control" and "sulfanilamide treated" cases, while striking, are not significant on checking by the statistical method.

Johnson and Meleney<sup>9</sup> have shown that it not only has a continuous inhibiting effect on the hemolytic streptococcus, the gas gangrene organisms, and other anaerobic bacteria, but has as well bactericidal and detoxifying action. In 20 per cent concentration it also has bacteriostatic action against *Staph. aureus* and in clinical use the 40 per cent suspension has a favorable effect on staphylococcus in pure or in mixed infections in vivo. It has been shown to be noninjurious to tissues and noninhibitive to the healing processes. Furthermore it never manifests any general toxicity to the patient. Meleney's success with its use in chronic burrowing undermining ulcers has been confirmed.<sup>25</sup> The rapid disappearance of the Welch bacillus in clinical gas gangrene as reported by Meleney<sup>18</sup> seemed to demonstrate the efficacy of zinc peroxide in that condition. Wright<sup>32</sup> reported the use of zinc peroxide in osteomyelitis and compound fractures as an adjunct to the closed plaster method of treatment. After débridement he dressed the wounds with zinc peroxide combined in the proportion of 3½ ounces of zinc peroxide mixed with 4 ounces of cod-liver oil. The wounds were then enclosed in plaster and not dressed for four weeks. On redressing there presented a healthy granulating wound in the process of epithelization and free from odor. The wound was then redressed as necessary. Caldwell<sup>2</sup> was able to save 4 of 5 animals with experimentally produced *Cl. welchii* infected compound fractures by the use of zinc peroxide in the wounds following débridement and irrigation. In the same series of experiments the use of sulfanilamide crystals instead of zinc peroxide resulted in the survival of only 4 of 19 animals.

In compound fractures the incidence of infection is high. If the primary surgical procedure does not remove all the injured tissue, or is delayed, infection approaches 100 per cent. A recent study of the bacterial flora of 200 acute traumatic wounds confirmed the impression that all wounds are contaminated.<sup>22</sup> The bacteriologic methods are fully reported in the previous paper. The bacteria found were: *Staph. aureus*, 104 times (52 per cent); hemolytic streptococci, 34 times (17 per cent); nonhemolytic streptococci, 53 times (26.5 per cent); green streptococci, 18 times (9 per cent); clostridia, 46 times (23 per cent); enterobacilli, 46 times (23 per cent); and the anaerobic gram-negative bacilli, 3 times (1.5 per cent). Dirty wounds were apt to yield hemolytic streptococci and the gas gangrene producing anaerobic bacilli more frequently than "clean" wounds. On the basis of these findings it seemed logical to us that since zinc peroxide is effective in vivo and in vitro against most of these organisms, its use in compound fractures and traumatic amputations would be advantageous and would reduce the number of infections. This paper is a report on 18 compound fractures and amputations treated with zinc peroxide. There are presented, as a control, 23 consecutive compound fracture cases treated similarly, except that zinc peroxide was not used. All cases were street

or industrial accidents. All the cases reported herein were seen within 3 hours of the injury.

#### PROCEDURE

On arrival in emergency ward the wound was usually first covered with several layers of an alcohol dressing, and the injured limb was placed in a splint. Tetanus (1,500 units) and gas bacillus (3,500 units) antitoxins were given. If there was gross, excessive bleeding, the bleeding vessels were clamped. Shock therapy was instituted if indicated and immediate blood grouping for transfusion done. If the patient was in shock, he was given morphine, kept warm with blankets, and given an infusion of hypertonic saline solution and dextrose. He was not moved until the blood pressure, pulse, and respirations were favorable. X-rays were always taken before and after reduction.

Next, the patient was taken to the operating room and anesthetized. The skin surrounding the wound was shaved and cleansed. The injured soft tissue was then widely exposed, with enlargement of the skin wound as necessary, and carefully cleansed. Cultures were taken of the devitalized, débrided tissue. An attempt was made to remove all foreign bodies, and to eliminate blood clots and dead and devitalized tissue. All surfaces were carefully irrigated with copious quantities of saline solution. Soap and water were used to clean greasy and dirt-stained tissues (the use of ether for this purpose was abandoned because of the resultant damage to the tissues).

After thoroughly cleansing the wound, the fracture were reduced. The fragments were retained properly by internal fixation or by single wire traction on the extremity. The wound was then flooded with a freshly prepared suspension of active zinc peroxide in sterile distilled water, filling all of the nooks, crannies, and recesses of the wound. The wound was then covered with a thin layer of cotton soaked in the zinc peroxide suspension, this in turn covered with cotton soaked in water, and sealed with several layers of fine meshed gauze impregnated with vaseline or zinc oxide ointment.

Three things are essential for the successful use of zinc peroxide:

1. It must be an effective preparation (*du Pont* zinc peroxide distributed by *Merek* and by *Mallinckrodt* is satisfactory).
2. It should be brought into contact with every part of the wound as a creamy suspension (about 40 per cent in sterile water).
3. It should be kept wet. Water facilitates the continuous production of fresh hydrogen peroxide as the oxygen is liberated from the zinc peroxide.

Redressing daily or every second day was done, depending on the individual case. For the first few days the zinc peroxide was found adherent to the tissues. This was left alone. However, on irrigating the wound and removing the loose particles and whatever exudate was present, one was struck by the minimal inflammatory reaction and

absence of edema. The wound was then redressed as before. The zinc peroxide did not appear to prevent the formation of granulation tissue, for its presence became quite obvious after the third to the fifth day. It rapidly increased, and as this happened, the adherent zinc peroxide became free and was washed away. When the wound was filled with granulation tissue, it was ready for secondary closure or grafting.

The results with this method of treatment are presented in Table II.

TABLE I  
CONTROL SERIES, 23 CASES COMPOUND FRACTURES (1938-1939)

NO. CASES	INJURY	DEATHS	INFECTIONS
4	Compound fractures of bones of skull; treatment consisted of debridement, elevation of bone fragments, and closure without drainage; cerebral concussion complicated 3 cases of the 4	0	0
2	Compound fractures of humerus, both in conjunction with compound fractures of skull and internal head injuries; one with simple fracture femur; both died, one 9 hours after arrival, the other 36 hours; the latter had infection in arm at time of death; treatment was for shock and débridement of wound; in the former there was not sufficient time for infection to develop	2	1 (50 per cent)
3	Compound fractures of radius and ulna; treatment: débridement, reduction and immobilization; one had associated multiple rib fractures, fractured pubis, and internal injuries; died 36 hours after arrival	1	0
3	Compound fractures metatarsals and phalanges; débridement and reduction and immobilization in 2; no infection; amputation of foot necessary in third; severe gas gangrene developed; <i>Staph. albus</i> , nonhemolytic streptococcus, <i>Cl. welchii</i> on culture; amputation through lower third of leg, given eighteen 20 c.c. doses anti-serum, x radiation, two blood transfusions, hydrogen peroxide, sulfanilamide; reinfection with gas gangrene; mid thigh amputation necessary; recovery	0	1 (33 per cent)
11	Compound fracture of tibia and fibula; four had internal fixation after débridement and no infection, seven had single wire traction and suspension in Thomas splint or plaster gutter; one developed a <i>Staph. aureus</i> infection which cleared, and another a <i>Staph. aureus</i> osteomyelitis which required partial osteotomy with fair functional result; a third case developed a trivial local infection; no cultures were taken, one death, a 73 year old white male from shock and myocardial failure	1	3 (27.2 per cent)
23 cases		4 deaths	5 infections or 21.8 per cent

TABLE II  
EIGHTEEN PEROXIDE TREATED CASES (1939-1940)

NO.	INJURY	CULTURE DEBRIDED TISSUE	TREATMENT	COMPLICATIONS	RESULT
<i>A. Ambulatory Cases</i>					
2551	Traumatic amputation phalanges	<i>Staph albus</i> , <i>B. proteus</i>	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3561	Traumatic amputation phalanges	<i>Staph albus</i> , <i>Staph. aureus</i> , <i>B. subtilis</i>	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3810	Traumatic amputation phalanges	<i>Staph albus</i> , hemolytic Streptococci microaerophile	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3874	Traumatic amputation phalanges	<i>Staph albus</i> , <i>Staph. aureus</i> , hemolytic streptococci, <i>M. tetrag.</i> , <i>B. cereus</i>	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
1877	Traumatic amputation phalanges	<i>Staph albus</i> , nonhemolytic streptococci anaerobic	Débridement, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3732	Compound fracture phalanges	<i>Staph albus</i> , nonhemolytic streptococci anaerobic	Débridement, reduction, splint, T.A.T., zinc peroxide cream dressings	None	Healed without infection
3885	Compound fracture dislocation phalanges	<i>Staph albus</i> , <i>B. subtilis</i> , nonhemolytic streptococci	Débridement, reduction, primary closure, T.A.T., splint	Inflamed, serousanguinous exudate; reopened; no cult.; zinc peroxide cream dressings	Infection resolved rapidly with zinc peroxide cream therapy; wound healed
3727	Compound fracture phalanges	<i>Staph albus</i> , <i>Staph. aureus</i> , hemolytic streptococci	Débridement, reduction, primary closure, splint, T.A.T.	Infection; reopened; culture, <i>Staph. aureus</i> , zinc peroxide cream dressings	Infection cleared with zinc peroxide cream therapy; wound healed

1099	Bullet wound dorsum hand; compound comminuted fracture proximal phalanx of thumb	<i>Staph. albus</i> , <i>Staph. aureus</i> , nonhemolytic streptococci anaerobic	Débridement, removal of bullet, T.A.T., and antigas serum, zinc peroxide cream dressings, splint	None	Healed without infection
<i>B. Hospitalized Cases</i>					
1972	Compound fracture 2-3-4 metacarpals; avulsion skin fingers and hand	<i>Staph. albus</i> , <i>M. tetrag.</i> , <i>Cl. tertium</i>	Débridement, T.A.T., antigas serum, zinc peroxide cream dressings	None	Successful skin graft; healed without infection
1811 II	Crushing injury foot; partial amputation	<i>Staph. albus</i> , hemolytic streptococci, <i>C. welchii</i>	Chopart amputation, skin flap prepared, T.A.T., antigas serum, zinc peroxide cream dressings	None; secondary closure skin flap	Healed without infection
1807 II	Traumatic amputation middle third humerus	<i>Staph. albus</i> , <i>B. subtilis</i> , hemolytic streptococci, <i>Cl. welchii</i>	Débridement, preparation of skin flap, T.A.T., antigas serum, zinc peroxide cream dressings	Death fourth day; myocardial failure	Stump not infected; swab culture immediately; P.M.: <i>Staph. albus</i>
2122-II	Traumatic amputation middle third arm by steel combs of wool-sorting machine; multiple puncture wounds above amputation site	<i>Staph. albus</i> , <i>B. anthracis</i> , hemolytic streptococci	Débridement, loose closure with rubber drainage, T.A.T., antigas serum, antianthrax serum, sulfanilamide, 16 Gm. in 4 days	Stump and lateral chest wall became purify; gelatinous slough; wound reopened; zinc peroxide cream dressing; culture fifth day; hemolytic streptococci, <i>Staph. albus</i>	Wound granulating and healing; ninth day developed right heart failure, followed by hemolytic streptococci pneumonia, then hemolytic streptococci meningitis; 49 Gm. sulfanilamide and sulfapyridine given without effect; died twenty-fourth day; stump not infected

TABLE II—CONT'D

NO.	INJURY	CULTURE DEBRIDED TISSUE	TREATMENT	COMPLICATIONS	RESULT
654-II	Compound fracture tibia and fibula, multiple lacerations, deep, of leg	No cultures taken	Debridement, T.A.T., antias serum, single wire traction, zinc peroxide cream dressings	Died fourth day, traumatic shock; myocardial failure	No infection at time of death
1114-H	Avalanche heel, lacerated masseter muscle, upper lip and gum; comminuted fracture maxilla into sinus; deep lacerations of neck	No cultures taken	Debridement, shock therapy, T.A.T., antias serum, boric acid compresses, 10 per cent mercuric iodine into maxillary sinus	Wounds infected, culture: <i>Staph. albus</i> , hemolytic streptococci; zinc peroxide cream irrigation and dressing	Infection cleared; secondary closure and plastic surgery
4077-II	Lacerations, lips, chin, and cheek with compound fracture maxilla into sinus, puncture wound through lower alveolar process	No cultures taken	Debridement, shock therapy, T.A.T., primary closure	Chin and cheek wounds infected; no cultures taken; zinc peroxide cream dressings and mouth irrigations	Suppuration ceased; zinc peroxide cream applied to alveolar process after extraction teeth upper maxillary; all wounds healed
1467	Extensive lacerations scalp with devitalization; fracture of right parietal bone	<i>Staph. albus</i> , <i>M. tetragenus</i> , hemolytic streptococci	Debridement, T.A.T., zinc peroxide cream; shock therapy	None	Granulated and healed without infection
1601	Multiple lacerations and gunpowder burns, head and face; compound fracture right parietal bone	<i>Staph. albus</i> , <i>Staph. citreus</i> , nonhemolytic streptococci	Debridement, elevation of depressed fragment, zinc peroxide cream dressings	None	Wounds healed without infection



## RESULTS

The control series of 23 consecutive compound fractures admitted to the hospital during 1938-39 are presented in Table I. This series is comparable to the inpatient cases in the zinc peroxide group. The outpatient record of the non zinc peroxide-treated compound fractures does not permit a comparison with the zinc peroxide cases treated as outpatients. In 16 cases of the control series no infection developed. In 2 other cases 1 patient died 9 hours and the second 36 hours after admission, and there was no clinical evidence of infection. Five cases (21.8 per cent) developed infection. In 7 cases the wounds were closed. Infection (gas gangrene) developed in 1 of these (14.2 per cent). In 16 cases the wounds were left open. Infection developed in 4 (25 per cent). In 1 the stump of an amputated arm appeared infected at the time of death, the second day after injury. The second was a mixed infection due to *Staph. aureus* and hemolytic streptococci. The third was a trivial infection from which no cultures were taken. The last case developed a *Staph. aureus* osteomyelitis. The differences in percentage of infections between the closed and open wounds is partly explained by the fact that only the most favorable cases, as regards degree of contamination and devitalization of tissue, were closed. The more serious and dirty wounds were left open. Four of the patients in this series died. There were no deaths attributed to infection.

The treated series covers a period of one year, beginning July, 1939, during which 18 cases of compound fractures received zinc peroxide locally in addition to surgery, splinting, and administration of tetanus and gas bacillus antisera. There were 10 injuries to the phalanges, 1 crushing injury of the foot, 1 fracture of the tibia and fibula, 2 traumatic amputations of the humerus, and 4 fractures of bones of the skull. In 13 patients the wounds were left open and treated with zinc peroxide, and no infections developed. From 5 of these hemolytic streptococci were cultured from the débrided tissue fragments, from 3, nonhemolytic anaerobic streptococci, and from 2, *Cl. welchii*. Staphylococci were present in conjunction with these organisms in every case. In 1 patient the wound was left open and treated with 10 per cent mercurchrome and boric acid compresses. Infection developed yielding hemolytic streptococci but cleared rapidly with the change to zinc peroxide applications. In 4 patients the wounds were closed following débridement and reduction, and each wound subsequently became infected. Two yielded hemolytic streptococci on preliminary culture; 1 also had an aerobic nonhemolytic streptococcus, and another, *B. anthracis*. In the fourth case no cultures were taken. After opening the wounds and treating them with zinc peroxide, the infections promptly cleared. There were 3 deaths in this series. Two were in men over 70 years of age and were attributed to uncontrollably severe

shock and myocardial failure. The third death was twenty-four days after the accident and was due to a hemolytic streptococcus, cerebrospinal meningitis, and pneumonia. Sulfanilamide and sulfapyridine were not effective. The wounds in all 3 patients were benign and healing at the time of death.

#### COMMENT

Zinc peroxide dressings bring about a prompt visible change in the appearance of the wounds treated. For the first two days the surface of the wound is gray with adherent particles of the zinc peroxide. One is struck by the absence of any swelling, redness, or other indication of inflammation. On the third or fourth day pinpoint granulations appear and rapidly spread over the entire wound surface. The new tissue is bright, shiny, red, and firm, and there is no evidence of the invasion or activity of micro-organisms. The change of dressings every day or every other day does not disturb the immobilization of the fracture. The dressing probably could be left much longer without changing. Meleney<sup>17</sup> has left zinc peroxide dressings as long as nine days in the perineal wound of an abdominoperineal operation. Wright<sup>29</sup> has left them sealed under plaster in compound fractures for four weeks.

Zinc peroxide does not interfere with the radiographic evidence of callus formation. Although it is radiopaque, it can be easily distinguished. It does not get lost in the interstices of the wound but is discharged by the proliferation of granulation tissue. Because it is not absorbed, it should not, of course, be used in wounds which are to be closed. In open wounds, however, with the use of zinc peroxide, serious infections with gas gangrene organisms, and other anaerobic bacteria, as well as with hemolytic streptococci and other susceptible organisms, are avoidable. Infections due to susceptible organisms respond rapidly when the drug is brought in apposition to the infected tissue. Zinc peroxide never manifests any general toxicity to the patient. Its use in compound fractures obviates the objectionable odors attendant upon the closed plaster method. While the series is small because of the termination of resident service, the results obtained are sufficiently encouraging to warrant further use of zinc peroxide prophylactically in the prevention of infection in compound fractures.

#### SUMMARY

1. The recent literature on compound fracture therapy is reviewed.
2. Traumatic wounds are always contaminated. The most virulent contaminating organisms are the hemolytic streptococci, the clostridia, and other anaerobic organisms, all of which are susceptible both in test tube and in vivo to zinc peroxide.
3. The results on 18 cases of compound fractures and traumatic amputations treated with zinc peroxide are analyzed. Thirteen wounds left open and treated with zinc peroxide healed without infection. One

wound left open and treated with 10 per cent mercurochrome and boric acid became infected. Infection promptly cleared with zinc peroxide. Four wounds closed primarily became infected; on reopening, zinc peroxide therapy rapidly cleared the infections in each case. In 23 "control" cases not receiving zinc peroxide treatment, the incidence of infection was 21.8 per cent.

4. The method of using zinc peroxide in these cases is given in detail.

5. Finally, a plea is made for the routine aerobic and anaerobic culture of all traumatic wounds. Precise knowledge of the bacterial flora contaminating such wounds is essential, not only for the anticipation of and the prevention of infection, but also for the proper evaluation of the results of treatment instituted to combat it.

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## TREATMENT OF FRACTURES IN THE NECK OF THE HUMERUS WITHOUT IMMOBILIZATION

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**F**RACTURE in the upper end of the humerus is a common occurrence in persons of advanced years, and until recently the permanent handicap which followed this injury was almost a foregone conclusion. Most of these fractures unite within a few weeks under any form of treatment, but with former methods as attention was directed to the fracture alone the end result in many instances was a poorly functioning limb. The disability not only was caused by adhesions and contractures which occurred in the shoulder joint from binding the arm to the chest, but also was due to prolonged immobilization of the other joints in the dressing.

In order completely to reduce and immobilize such a fracture, and to prevent much disabling tightness of the shoulder, we formerly used plaster of Paris spicas or body casts, which held the lower fragment of the humerus in the abducted position to meet the upper fragment. Fractures without displacement also were immobilized in partial abduction, in order to prevent the disability which resulted from binding the arm to the chest. However, although these body casts maintained complete reduction and prevented the disabling contracture of the shoulder caused by the Velpeau dressing, their heavy weight and awkwardness were a great burden to these older patients. Furthermore, such complete immobilization of the entire limb in plaster of Paris left the patients with the same muscular weakness and stiffness of joints which bandaging the limb to the body had produced. Our dissatisfaction with results prompted us to treat this injury in an entirely different manner.

### RECENT DEVELOPMENTS

Watson-Jones<sup>1</sup> has simplified the treatment of fractures in this location by disregarding the customary classification of the anatomical and surgical necks of the humerus, dividing them into the abduction and adduction forms. The essential feature of reduction in most instances is moving the distal or shaft fragment to meet the proximal or immovable fragment, by adduction or abduction according to the displacement. The fragments will remain in a relatively normal position after reduction, providing the arm hangs at the side of the body, without support to the elbow. The hanging position for fractures in the neck of the humerus is rational. In discussing fractures above the insertion of the pectoralis major, Griswold<sup>2</sup> calls attention to the squeezing effect on the fragments

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to the arm and forearm with the elbow held at a right angle; a loop of bandage is fastened to the plaster at the wrist, and this bandage is passed around the neck to form a sling. While wearing this the patient performs relaxed swinging exercises frequently, these exercises beginning the day after injury. This method was found to be a decided improvement. The atrophy caused by complete immobilization was prevented, and early exercises prevented limitation of abduction and rotational movements at the shoulder. A number of impacted fractures then were treated by early exercises alone, with excellent results.

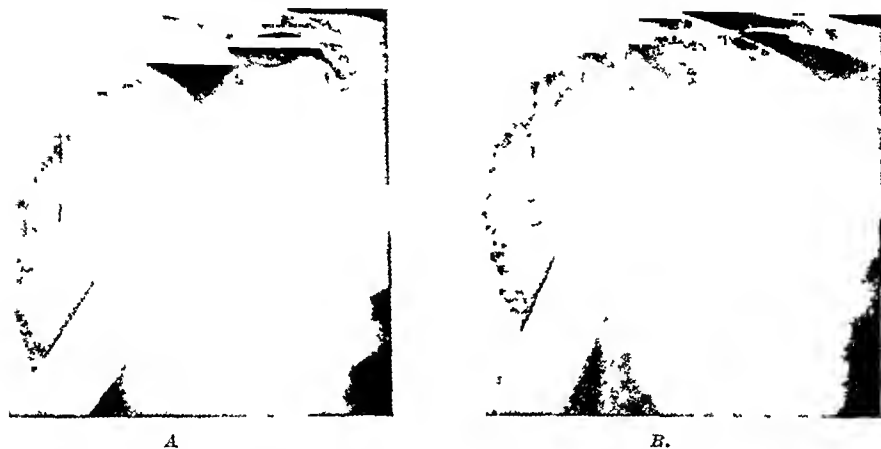


Fig 2—A H M Severe fracture before treatment. Note the rotation of the head, and extreme displacement of the shaft of the humerus. B Same fracture as shown in A, after application of a simple sling from the neck to the wrist. The alignment of the fragments, although not perfect, was satisfactory and union with good function was secured by relaxed movements without immobilization.



Fig 3—Relaxed abduction and circumduction exercises of patient whose x-ray films are shown in Fig 2. This photograph was made on the third day after injury. Note accompanying injury to the soft structures.

by longitudinal muscles while traction is made with the arm held parallel to the body. Howard and Bloesser<sup>3</sup> have shown that tension of the tendon of the long head of the biceps controls the upper fragment by its pressure in the bicipital groove while the arm hangs by the side of the body, and the weight of the arm itself causes slight traction. Much less traction is needed in the adducted position than while the arm is held in abduction. Occasionally, in fractures high in the neck with marked adduction angulation, reduction can be obtained and maintained only by wide abduction. Obviously, in these cases the hanging position is contraindicated.

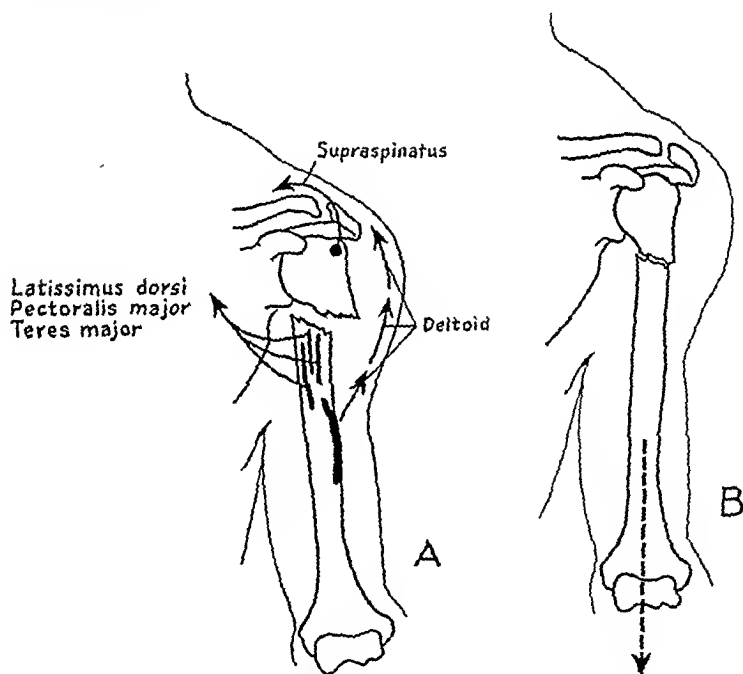


Fig. 1.—A. Typical fracture in the neck of the humerus, showing effect of muscular attachments in displacement of the fragments. B. Satisfactory alignment produced by the traction effect of the weight of the arm in the hanging position.

#### PERSONAL EXPERIENCES

For several years I examined fractures in the neck of the humerus under the fluoroscope to determine definitely which cases were impacted. The routine treatment for impacted fractures was rest in a sling for two weeks, after which activity was encouraged; in a number of instances the patients were observed to have commenced exercises of their own accord, as they had very little pain. Later the simple form of hanging cast for ambulatory traction as originally advocated by Caldwell<sup>4</sup> and subsequently recommended by Griswold and others was used. Caldwell's method<sup>5</sup> is a departure from the usual routine of complete and continuous immobilization, and consists of a heavy plaster of Paris cast applied



movements at the shoulder joint. Use of the hand and elbow for light occupations about the home is encouraged. The psychological element of this treatment also is helpful, as relaxed voluntary movements overcome the fear and consequent delay in recovery which are common after



Fig. 5.



Fig. 6.

Fig. 5.—Simple sling from the neck to the wrist used for these fractures. The fragments are controlled by the traction from the weight of the arm, and by muscle tension. Note that the elbow is held at a right angle, and that this sling produces slight abduction at the shoulder.

Fig. 6.—Double exposure. Flexion and extension at the shoulder secured by the "sawing" exercise.



Fig. 7.



Fig. 8.

Fig. 7.—"Dipping" exercise, with the shoulder relaxed in stooping.

Fig. 8.—Circumduction by swinging movements, with the arm hanging in abduction. The patient must bend forward as far as shown. These relaxed movements are performed completely by the average patient within six weeks after injury. In the case shown there was 90 per cent of the normal range of voluntary movements after nine weeks.

The favorable experience with impacted fractures treated by immediate voluntary motions, without immobilization or even a hanging cast, led to treating the unimpacted fractures in the same manner. This treatment was prompted by the observation that the fragments in unimpacted cases were held relatively immobile by muscle spasm, and that early relaxed movements by the patient as in stooping did not disturb the fragments or cause pain. There were numerous cases in which considerable movement of the fragments was noted under the fluoroscope, yet even in these instances a wide range of shoulder motions was obtained within a short time because the arm was treated without the customary immobilization. Later several extreme cases in which the fragments were markedly displaced were manipulated, and after reduction were treated in like manner. It was observed that cases of fractures caused by such indirect violence as falling on the outstretched hand recovered in a relatively shorter time, although comminuted fractures which were caused by direct force as falling on the side of the shoulder usually were followed by a longer period of disability on account of greater soft tissue injury. All of the fractures united within eight weeks.



Fig. 4 A and B—J. C., aged 68 years. Typical case, the fragments being moderately impacted but movable. Complete restoration of function after ten weeks. X-ray film five weeks after injury shows union.

These results demonstrated that easy, relaxed movements prevent muscular atrophy and limitation of shoulder function, and at the same time do not interfere with union. The patient will not move the limb further than to the point of discomfort, which range increases day by day, and thus there is no liability to displace the fragments. Absolutely no passive movements are given, as manipulation would interfere with union. In the upright position the arm cannot be raised forward or outward voluntarily, but, in stooping, the arm can be swung by relaxed



Fig. 12.

Fig. 12—M. H., 50 years of age. Good range of relaxed movements at end of six weeks, 75 per cent of normal strength and movements at end of twelve weeks.

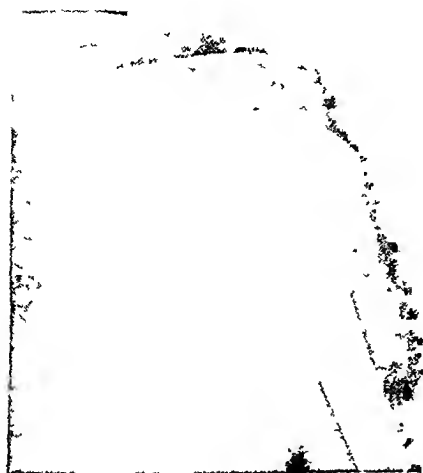
Fig. 13—C. M., 86 years of age. Satisfactory range of relaxed movements in six weeks, 75 per cent of normal range at end of eight weeks; 90 per cent of normal after five months.

Fig. 14—B. C., 69 years of age. Excellent cooperation and relaxed movements. Result at five weeks was 50 per cent of normal function. No further follow-up.

Fig. 13.

Fig. 14.

any form of immobilization. In all of the instances there is a progressive return of shoulder motions, and union occurs as rapidly as in those treated by complete immobilization. Even in severe cases the sling from the wrist to the neck can be discarded after three or four weeks. Obviously a good result depends upon the complete cooperation of the



A.



B.

Fig 9 A and B—L G, aged 61 years. Fracture without impaction. Within six weeks after injury there was a free range of the relaxed movements and firm union.



Fig. 10.



Fig. 11.

Figs. 10 and 11.—Functional result twelve weeks after fracture shown in Fig 9. There is a complete range of abduction and of external rotation.

patient in following out the prescribed exercises thoroughly and often, and repeated instructions and check-up by the attending physician are necessary. In all of the fifteen cases I treated and under my supervision



Fig. 12.

Fig. 12.—M. H., 50 years of age. Good range of relaxed movements at end of six weeks; 75 per cent of normal strength and movements at end of twelve weeks.

Fig. 13.—C. M., 86 years of age. Satisfactory range of relaxed movements in six weeks; 75 per cent of normal range at end of eight weeks; 90 per cent of normal after five months.

Fig. 14.—B. C., 69 years of age. Excellent cooperation and relaxed movements. Result at five weeks was 50 per cent of normal function. No further follow-up.

Fig. 13.

Fig. 14.



Fig. 15

Fig. 16.

Fig. 17.

Fig. 15.—L. K., 72 years of age. Probably impacted. Free from pain with voluntary abduction to 90 degrees in three weeks; 75 per cent of normal strength and motion after six weeks. No further follow-up.  
 Fig. 16.—A. F., 60 years of age. Voluntary movements 50 per cent of normal six weeks after injury; 90 per cent of normal at end of fifteen weeks.  
 Fig. 17.—H. M., 54 years of age. Seventy-five per cent of normal range of movements and returned to work as night watchman four weeks after injury.



Fig. 18.

Fig. 18—S. T., 63 years of age. Ninety per cent of normal range of movements at end of eight weeks.

Fig. 19—S. T., 80 years of age. Good cooperation in relaxed exercises, 75 per cent of normal range of movements by tenth week.

Fig. 20—B. Y., 70 years of age. Average range of relaxed movements by end of six weeks. Continued improvement, with 66 per cent of normal function on last visit at ninth week.

Fig. 19.

Fig. 20.

the functional results were good. In three cases even without complete reduction the function was satisfactory on account of the preservation of movements.

#### SUMMARY

A simple and effective treatment for a majority of fractures in the neck of the humerus has been described. Its chief feature is the preservation of movements in the limb, in contrast to the former customary immobilization which often was followed by permanent limitation of movements and weakness. This method consists of supporting the wrist with a sling and encouraging immediate relaxed exercises. It is an exception to the general rule that all fractures must be immobilized for at least a preliminary period. Careful observation shows that the method described does not cause delay in union. It is recommended for all fractures in the neck of the humerus, except when fracture-dislocation or decided displacement exists.

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## TIBIAL EPIPHYSIOTOMY FOR SEVERE GENU RECURVATUM

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THE correction of severe paralytic genu recurvatum is a major problem. Many surgical methods advocated have consisted of soft tissue corrective work which eventually has often allowed regression to the original deformity by action of the original causative factors.

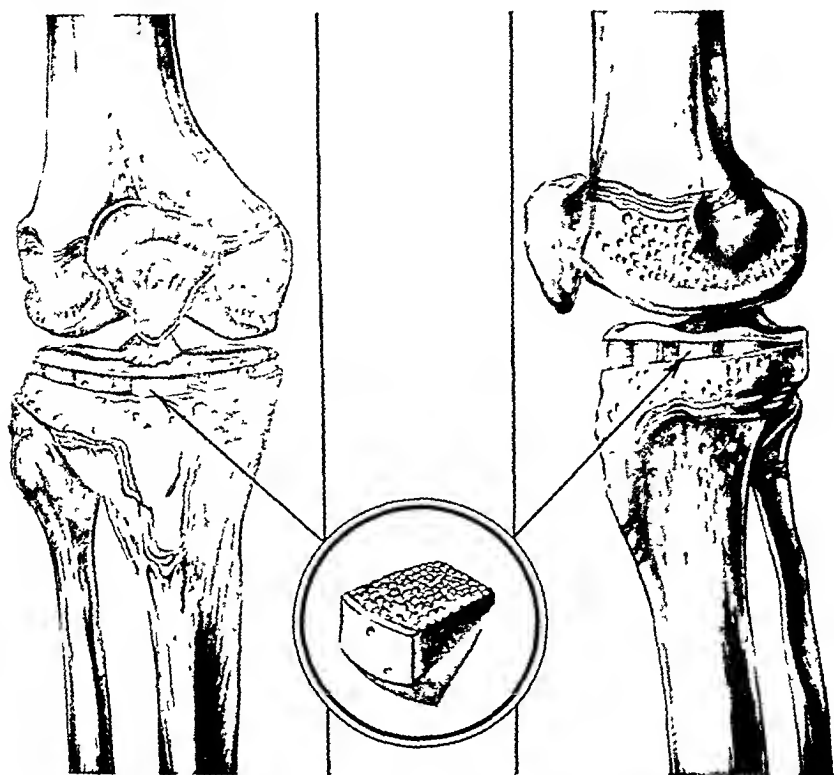


Fig. 1.—Tibial epiphysiectomy with wedge grafts from tibial crest.

The procedure here presented arose from observation of the necessity of splinting fractured tibial spines in complete knee extension to prevent flexion deformity. Recent work<sup>1</sup> has confirmed the belief that the tibial spines and anterior articular surfaces are the only bone block to extension of the knee, the other limiting factors being soft tissue (capsule, lateral and cruciate ligaments) and muscle action. Brett<sup>2</sup> has described a method of correction by elevation of the anterior articular surfaces

of the tibia in the mature adult after closure of the epiphyses. A comprehensive report<sup>3</sup> has demonstrated that all growth in length of the long bones occurs on the diaphyseal side of the epiphyseal line and that articular cartilage growth is at the articular surface.



Fig. 2.—Paralytic genu recurvatum. *A* Prior to operation. *B* Twelve weeks post-operatively.

Since experience has shown that corrective surgical procedures should make use of all possible adaptive processes of the growing child, such procedures should be done at the earliest possible time after the indication becomes evident when benefit and not harm can be done to the individual. As a logical corollary to the studies mentioned, a linear tibial epiphysiostomy seemed an ideal simple method of correcting the

deformity of genu recurvatum by using the normal mechanism of the knee joint to prevent hyperextension and to establish correct alignment of the leg. The fear of epiphyseal injury in this area has been dispelled and neither the epiphyseal growth area nor the joint is disturbed.



Fig 3—X-ray in complete extension. A. Prior to operation. B. Twelve weeks post-operatively.

The procedure used consists of a longitudinal incision over the anterior aspect of the knee and upper half of the tibia. The patellar tendon is sectioned, the joint inspected, and the epiphysis and upper third of the tibia exposed. With a wide thin osteotome, a linear osteotomy is made across the middle of the epiphysis parallel to the articular

surface and extending almost to the posterior cortex of the epiphysis. This is gently pried apart anteriorly and wedge-shaped grafts taken from the tibial crest are inserted firmly to maintain anterior distraction. The recurvatum is corrected entirely at time of surgery. The patellar tendon is sutured, the wound closed, and a long leg cast applied with the knee in moderate flexion. Immobilization for about twelve weeks in children gives firm union.

The case presented is that of a 10-year-old girl with a completely flail leg which has shown remarkable increase in stability following this procedure but which will require additional stabilizing procedures on the foot, ankle, and possibly the hip.

A method of correction of genu recurvatum is presented, using the normal physiologic knee-joint mechanism to block hyperextension by rigid structures, which is performed during the growth period, thus obviating long-continued brace use and increase to more severe deformity during the wait for epiphyseal closure.

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## BLASTOMYCOSIS OF BONE

A REVIEW OF 63 COLLECTED CASES, OF WHICH 6 RECOVERED\*

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IN REVIEWING the literature on generalized blastomycosis we have been able to collect 63 cases which showed evidence of bone involvement. Six of these patients recovered after treatment, 3 were not followed sufficiently long to determine their end result, and 53 died of the disease. The detailed case report accompanying this article (page 939)<sup>37</sup> records the history of a seventh patient with bone blastomycosis who was cured after prolonged treatment. Because of the usually poor therapeutic results, we believed it of interest to summarize our present knowledge of this type of infection and to outline certain studies which we have found valuable in the diagnosis, prognosis, and treatment of the disease.

Although the cutaneous type of blastomycosis is familiar to most physicians, the generalized form of the disease is less easily recognized unless it begins with characteristic skin lesions. However, the first signs of infection may be the presence of abscesses in the subcutaneous or deeper tissues. These lesions may resemble either the tuberculous-like "cold" abscess or may be of the acute pyogenic inflammatory type. More commonly the initial symptoms are pulmonary, characterized by the development of a cough productive of small amounts of mucoid sputum. Pleural pain may be the presenting symptom. In 13 patients with bone involvement the primary complaint was arthritic pain in the back or about the joints of the extremities. In 2 cases with bone lesions the initial diagnosis was "articular rheumatism."

In the majority of cases the course of the disease is that of a chronic febrile illness with progressive loss of weight and strength, a moderate secondary anemia, and leucocytosis. The pulmonary symptoms may dominate the picture, the patients having cough, varying amounts of sputum, hemoptysis, or pleural pain. Often there occurs progressive development of soft tissue abscesses with or without bone involvement. In allergic patients these abscesses may develop very rapidly, show signs of acute inflammation, and contain a bloody tenacious exudate. If the degree of allergy is less marked, the "cold" abscesses contain thick purulent material. If these break through the skin or are drained, they frequently lead to the formation of chronic sinuses which drain a thin yellow pus. The foci of infection in the bones of the extremities

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(Table I), if located near the epiphyseal lines, may extend into joints and form pyarthroses which in turn may drain to the surface through chronic sinuses. Paravertebral or psoas abscesses may form from extension of spine lesions (Table I). Usually the patient succumbs with

TABLE I  
DISTRIBUTION OF BONE AND JOINT LESIONS IN 63 REPORTED CASES OF  
GENERALIZED BLASTOMYCOSIS

LOCATION	NO. OF CASES	LOCATION	NO. OF CASES	LOCATION	NO. OF CASES
Vertebra*	25	Shoulder	1	Hip	3
Skull	21	Elbow	7	Knee	11
Ribs	19	Ulna	4	Tibia	16
Sternum	8	Radius	2	Fibula	6
Clavicle	4	Carpus	10	Patella	3
Scapula	2	Metacarpals	5	Tarsus	12
Pelvis	5	Phalanges	3	Metatarsals	10
Humerus	4	Femur	5	Toes	3

\*Paravertebral abscesses were present in 14 cases.

a widespread infection involving not only his skin, soft tissues, lungs, and bones but also the lymph nodes, spleen, liver, and kidneys. In some cases the central nervous system, prostate, heart, and peritoneum have been affected.

Our present concepts of the gross and microscopic pathologic changes in this disease are based largely on Stober's<sup>54</sup> description of the necropsy findings in a large series of cases reported from Chicago. The skin and respiratory tract are the chief portals of entry, and from either site there is a marked tendency for the disease to spread by direct extension or by contiguity of tissue. It is well to note here that two of Stober's cases developed systemic blastomycosis directly following curettement of skin lesions. The pulmonary infection appears first in the bronchi and these lesions spread to become associated with bronchopneumonia in the adjacent lung. The pleura, the pericardium, and the mediastinal lymph nodes may be involved by lymphatic extension from the pulmonary focus. Having entered the blood stream from the lung or the skin, the organism may be disseminated throughout the body to produce multiple metastatic foci. These, in their turn, may cause further blood stream infection and reinfection of the lungs and other tissues. By this means the skin, the subcutaneous tissue, the muscles and bones and all the important viscera may be involved.

The tissue reaction to the presence of the organism may be quite variable. Usually the infected areas show round-cell infiltration, not infrequently associated with polymorphonuclear leucocytes, or giant cells or both. However, blastomycetes may be found in tissues showing no histologic change, or the only alteration noted may be small areas of necrosis. Extensive necrosis with abscess formation is common. The typical gross lesions of the disease are the cutaneous ulcers, the deep and superficial abscesses, and the tubercle-like nodules in the viscera.

In bone the infection may be a localized or a diffuse osteomyelitis, a periostitis, or, if a joint is involved, an arthritis. In the long bones the primary focus usually is found at the epiphyseal line and at times the areas of bone destruction resemble infarcts. Microscopic sections show many fungi invading the marrow compartments with the usual cellular reaction, necrosis of the marrow cells, and bone destruction. As the bone partitions disappear, the separate foci may become confluent and form abscesses with separation of sequestra. The joint usually is infected by extension from a focus in adjacent bone through the synovium or cartilage.

The clinical diagnosis of blastomycosis may be suspected from the history and the physical findings. However, a similar picture can be produced by infections with other fungi, tuberculous osteomyelitis, and tertiary syphilis of bone. One of our patients, with lesions of the chest wall and ulna, was thought to have an Ewing's sarcoma until further studies disproved this impression. To establish an unequivocal diagnosis, the clinical impression must be supplemented by laboratory studies.

The isolation and identification of *Blastomyces dermatitidis* from infected secretions or exudates is proof of infection and should be attempted in all cases. The characteristic double-contoured organisms usually can be seen by direct microscopic examination of unstained material and the diagnosis can be confirmed by finding the organisms in fixed tissue biopsy sections stained with hematoxylin and eosin. Tissue examination and cultures, however, are time consuming and we believe that aspiration, drainage, curettage and biopsy often are best deferred until the patient's allergic reaction has been determined by skin tests with a vaccine made from heat-killed *Blastomyces*. This test and the complement fixation test to be described are also of diagnostic value.

The skin tests are done with a heat-killed vaccine. This vaccine is prepared by suspending, in sterile saline solution, the yeastlike organisms from a culture of *Blastomyces dermatitidis* grown on blood agar at 37° C. This suspension is centrifuged in a Hopkin's tube and the sediment suspended in enough saline solution to make a 1:1,000 dilution by volume. The standardized suspension is heated to 60° C. for four hours and tested for sterility by heavily inoculating a blood agar slant and incubating at 37° C. for at least ten days. Trieresol, 0.35 per cent, is added as a preservative. This material is used for skin testing by injecting 0.1 c.c. intracutaneously. Usually an area of erythema appears about the site of injection within fifteen to twenty minutes. This reaction is not specific and is found in patients having pulmonary disease of other types. The characteristic positive reaction, beginning after twelve to twenty-four hours and reaching a maximum in two to four days, resembles closely a positive tuberculin reaction. In very allergic patients a sterile abscess may form at the site of inoculation. The occurrence of a

positive reaction may be taken as presumptive evidence of the presence of a blastomycotic infection and this diagnosis is strengthened further by finding of complement fixing antibodies in the serum of the patient.

The complement fixation test specific for *Blastomyces dermatitidis* has been described by one of us (D. S. M.),<sup>38</sup> and can be done in any laboratory equipped to do blood Wassermann reactions. The proportions of material and reagents are the same as used in the Wassermann test except for the substitution of a fungus suspension for the beef-heart antigen. Both of these procedures, i. e., the test for sensitivity to heat-killed *Blastomyces* vaccine and the complement fixation test, can and should be carried out as initial studies on patients suspected of having blastomycosis.

When reviewing the reported cases of blastomycosis, one frequently encounters instances where the diagnosis is based on the finding of the typical double-contoured round or oval bodies in secretions or exudates. These organisms should always be searched for, although from a diagnostic viewpoint the demonstration of organisms *Blastomyces dermatitidis* in secretions or exudates should not be considered unequivocal proof of blastomycosis. Benham has emphasized the fact that other fungi causing generalized lesions may appear as rounded bodies in tissue fluids. Some physicians, unfamiliar with the appearance of the fungus, have had some difficulty in distinguishing between these organisms and fat globules, disintegrating white blood cells and artefacts in sodium hydroxide preparations.

In addition to these studies, it is important to obtain roentgenograms of the chest in all cases of suspected infection because the lungs are the most common portal of entry of the fungus. Roentgenograms also may be made of any bone thought to be involved by the infection and particular attention should be paid to the possibility of spine lesions in patients who complain of backache. Plates should be taken at four- to six-week intervals to follow the progress of the bone lesions. In the case of a solitary bone lesion, it may be difficult for the roentgenologist to differentiate between tuberculous osteomyelitis, a primary osteoclastic tumor (such as Ewing's sarcoma and myeloma), and gumma of bone. However, when there are multiple bone lesions, a roentgenologic diagnosis of blastomycosis can be suspected. Well-localized, sharply defined destructive processes in the metaphyses, when multiple, suggest blastomycosis rather than the other conditions listed above. It has been stated that roentgenologic differentiation between blastomycosis and coccidioidal granuloma is difficult if not impossible.

As in any chronic debilitating illness, general hygienic measures are of first importance in the treatment of patients having generalized blastomycosis. Patients having this disease usually are individuals whose economic status is poor and who have been on an inadequate diet for months or years. Bed rest and an adequate diet are essential. The



diet should be supplemented by the administration of cod liver oil, large quantities of orange or tomato juice, and brewers' yeast. Anemia, if present, should be treated appropriately. The administration of potassium iodide is best deferred and the care of the local lesions should be purely palliative and conservative until the diagnosis has been established and the patient's allergic status determined.

The skin test with *Blastomyces* vaccine serves not only as a diagnostic procedure but also as a means of determining whether or not the patient should be desensitized. If the vaccine produces a sterile abscess, desensitization should be started with a dose of 0.1 c.c. of a 1:1,000 dilution of the vaccine (a 1:1,000,000 dilution of the original material). This is administered no more frequently than every other day and the dosage is kept below the point of causing a local or general reaction. Less sensitive patients can be started with a higher initial dosage. After the degree of allergy has been reduced, as judged by skin testing, iodides may be administered cautiously. We usually give a saturated solution of potassium iodide; beginning with 3 drops t. i. d. and increasing 1 drop per dose every day until tolerance is reached. In the case of an exacerbation of symptoms following the taking of iodides, the drug should be discontinued promptly and further attempts made to desensitize the patient. Complete desensitization is not thought necessary; however, the *Blastomyces* vaccine should be given until iodides are tolerated without unfavorable reaction. Beyond this the patient's need for the repeated administration of vaccine may be prescribed according to the judgment of the physician.

The care of the local lesions is best limited to conservative measures until desensitization is well under way and the administration of iodides has been started. Aspiration of deep or superficial abscesses may be done early when this procedure is necessary to establish a diagnosis, but it is best deferred until after medical treatment has been given. Open drainage of abscesses, curettage of ulcers or sinuses, and sequestrectomy are thought to be contraindicated in generalized blastomycosis by some observers. We believe that these procedures may be necessary at times, but that they should not be done until partial desensitization has been accomplished and iodides have been administered. Although amputation has been reported as curing at least one patient and may be indicated when the bones of the foot and ankle have been extensively damaged, the generalized nature of the infection should be kept in mind and this procedure used only as a last resort. In our experience we have encountered one patient with blastomycosis of bone who showed no evidence of skin sensitivity to *Blastomyces* vaccine. The treatment in this case is recorded in a subsequent report (page 939).<sup>37</sup>

Potassium iodide was given to all six patients who recovered from bone blastomycosis (Table II). Three of these also received heliotherapy which was believed to be beneficial. Two patients were given

TABLE II

## CASES OF GENERALIZED BLASTOMYCOSIS WITH BONE LESIONS WHICH RECOVERED

1. Herrick:<sup>23</sup> White, female, 24 years of age. Onset with rheumatic pains in left gluteal region. Subsequently developed seventy nine different lesions which in some instances, as in the case of the fingers, destroyed bone. Treated with potassium iodide by mouth and drainage of the local foci. No improvement until moved residence to California and lived out of doors. Recovery after an illness of three years' duration.
2. Boughton and Stober:<sup>4</sup> White, male, 29 years of age. Onset with pain in the chest, cough, fever, and weakness. The dorsum of the feet became swollen and tender and the initial diagnosis was "rheumatism." Total of twenty four lesions developed, including multiple abscesses and foci in the upper and lower ends of the right tibia. Treated first with potassium iodide for two and one half months but without improvement until blastomyces vaccine given. The latter caused inflammatory reaction about lesions but was followed by healing. Roentgenograms showed evidence of bone healing and recovery after further treatment with potassium iodide and vaccine. Reported as apparently well eighteen months after the onset of first symptoms.
3. Marshall:<sup>35</sup> White, female, 50 years of age. Onset with generalized weakness, loss of weight, and swelling of the right foot. Skin lesions appeared followed by afternoon elevations of temperature. Roentgenograms showed osteomyelitis of the metatarsals, osteoporosis of the cuboid, astragalus, and both malleoli. Treated with x ray therapy over the skin lesions, potassium iodide, and sun baths. Gradual recovery occurred although several new nodules appeared after starting treatment. It was thought that the daily sun baths were largely responsible for recovery, although one of the attending physicians ascribed the improvement to x ray therapy. After a winter in Florida, patient was apparently well one year after the onset of the infection.
4. Gillies:<sup>19</sup> White, male, 15 years of age. Onset with sore throat, hoarseness, cough, expectoration, and loss of weight. About the same time the left foot became swollen and three weeks later a draining sinus developed. Roentgenograms of the chest showed an infiltration of the left lung and films of the foot revealed an osteomyelitis of the tarsus. Six months later the foot was amputated and blastomyces found in the specimen. Meanwhile ulcers had developed on the right arm and leg. Potassium iodide was started nine months after onset and heliotherapy intensified. The patient was apparently well one year after the onset of symptoms and has remained so for six years.
5. Bergstrom, Nugent, and Snider:<sup>4</sup> Colored, male, 49 years of age. Onset with a "boil" on his leg. Multiple skin lesions developed and roentgenograms showed foci in the bones of one hand, in the left maxilla, and in the bones of both feet. Treated with neoarsphenamine, potassium iodide in milk, antimony and potassium tartrate intravenously, and with 3 c.c. of colloidal copper intramuscularly every five days for twenty doses. Five per cent iodine ointment was used on the local lesions. No improvement until the administration of the colloidal copper intramuscularly, but thereafter no new lesions appeared and those present began to heal. Ten months after discharge all lesions had healed except a sinus over one heel.
6. Martin and Smith:<sup>33</sup> White, female, 27 years of age. Onset with a fall causing a back injury and a broken arm. Shortly thereafter developed a cough with hemoptysis and had an elevated temperature. Hospitalized with a pulmonary infection diagnosed as blastomycosis. Improved under administration of blastomyces vaccine, potassium iodide, and the chest lesion cleared up. About this time was found to have blastomycosis of the uterus and tubes and these organs were removed.<sup>21</sup> Subsequently there developed a destructive process in the twelfth thoracic vertebra followed by a paraplegia. This improved following laminectomy and further courses of blastomyces vaccine and potassium iodide. Her complement fixation test became negative and she has remained clinically well for five years.

Blastomyces vaccine with apparent benefit and in one case x-ray therapy was thought to have been responsible for the improvement. There is a recent report of a patient who recovered after treatment with potassium iodide, antimony, and potassium tartrate intravenously, and 3 c.c. of colloidal copper intramuscularly every five days for twenty doses. The last drug was believed to have caused the patient's improvement. The local application of a copper sulfate solution would appear to be of little value in cases of the generalized disease. Although studies have suggested the possible value of intravenous gentian violet in treating this infection we have found no reported instance of its clinical trial.

The prognosis of the majority of patients having blastomycosis with bone lesions is poor, especially in those individuals who have a high titer of complement fixing antibodies. Undoubtedly there are many patients who have recovered from this disease whose case records have not been reported in the literature. It is to be hoped that in the future more cases of clinical cures will be recorded and that a better knowledge of the factors responsible for recovery can be obtained.

#### SUMMARY

1. In a review of the 63 reported cases of bone blastomycosis, there were found 6 patients who recovered from the disease.
2. The locations of the bone lesions are tabulated and a résumé given of the cases which recovered.
3. Our present knowledge of this infection is summarized.
4. The problem of diagnosis is discussed and the suggestion made that patients having bone lesions be partially desensitized to *Blastomyces* vaccine before beginning treatment with either iodides or surgery.

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TABLE II

## CASES OF GENERALIZED BLASTOMYCOSIS WITH BONE LESIONS WHICH RECOVERED

1. Herriek:<sup>23</sup> White, female, 24 years of age. Onset with rheumatic pains in left gluteal region. Subsequently developed seventy-nine different lesions which in some instances, as in the case of the fingers, destroyed bone. Treated with potassium iodide by mouth and drainage of the local foci. No improvement until moved residence to California and lived out-of-doors. Recovery after an illness of three years' duration.
2. Boughton and Stober:<sup>6</sup> White, male, 29 years of age. Onset with pain in the chest, cough, fever, and weakness. The dorsum of the feet became swollen and tender and the initial diagnosis was "rheumatism." Total of twenty-four lesions developed, including multiple abscesses and foci in the upper and lower ends of the right tibia. Treated first with potassium iodide for two and one-half months but without improvement until blastomyces vaccine given. The latter caused inflammatory reaction about lesions but was followed by healing. Roentgenograms showed evidence of bone healing and recovery after further treatment with potassium iodide and vaccine. Reported as apparently well eighteen months after the onset of first symptoms.
3. Marshall:<sup>35</sup> White, female, 50 years of age. Onset with generalized weakness, loss of weight, and swelling of the right foot. Skin lesions appeared followed by afternoon elevations of temperature. Roentgenograms showed osteomyelitis of the metatarsals, osteoporosis of the cuboid, astragalus, and both malleoli. Treated with x-ray therapy over the skin lesions, potassium iodide, and sun baths. Gradual recovery occurred although several new nodules appeared after starting treatment. It was thought that the daily sun baths were largely responsible for recovery, although one of the attending physicians ascribed the improvement to x-ray therapy. After a winter in Florida, patient was apparently well one year after the onset of the infection.
4. Gillies:<sup>10</sup> White, male, 15 years of age. Onset with sore throat, hoarseness, cough, expectoration, and loss of weight. About the same time the left foot became swollen and three weeks later a draining sinus developed. Roentgenograms of the chest showed an infiltration of the left lung and films of the foot revealed an osteomyelitis of the tarsus. Six months later the foot was amputated and blastomyces found in the specimen. Meanwhile ulcers had developed on the right arm and leg. Potassium iodide was started nine months after onset and heliotherapy intensified. The patient was apparently well one year after the onset of symptoms and has remained so for six years.
5. Bergstrom, Nugent, and Snider:<sup>4</sup> Colored, male, 49 years of age. Onset with a "boil" on his leg. Multiple skin lesions developed and roentgenograms showed foci in the bones of one hand, in the left maxilla, and in the bones of both feet. Treated with nearsphenamine, potassium iodide in milk, antimony and potassium tartrate intravenously, and with 3 c.c. of colloidal copper intramuscularly every five days for twenty doses. Five per cent iodine ointment was used on the local lesions. No improvement until the administration of the colloidal copper intramuscularly, but thereafter no new lesions appeared and those present began to heal. Ten months after discharge all lesions had healed except a sinus over one heel.
6. Martin and Smith:<sup>30</sup> White, female, 27 years of age. Onset with a fall causing a back injury and a broken arm. Shortly thereafter developed a cough with hemoptysis and had an elevated temperature. Hospitalized with a pulmonary infection diagnosed as blastomycosis. Improved under administration of blastomyces vaccine, potassium iodide, and the chest lesion cleared up. About this time was found to have blastomycosis of the uterus and tubes and these organs were removed.<sup>21</sup> Subsequently there developed a destructive process in the twelfth thoracic vertebra followed by a paraplegia. This improved following laminectomy and further courses of blastomyces vaccine and potassium iodide. Her complement fixation test became negative and she has remained clinically well for five years.

## SYSTEMIC BLASTOMYCOSIS

### REPORT OF A CASE WITH UNUSUAL IMMUNOLOGIC FINDINGS, WELL TWO YEARS AFTER ONSET\*

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#### INTRODUCTION

THE treatment of blastomycosis (American form) varies with the individual patient, depending upon the extent of the infection, the degree of allergy developed by the patient, and the locality and nature of the individual lesions. The following case is reported because the patient presented an immunologic picture markedly different from that usually seen in blastomycosis, which necessitated a radical departure from the treatment usually used in this disease.

#### CASE REPORT

H. M. M. (History No. A5847), a white farmer, 30 years of age, was admitted to Duke Hospital on Aug. 8, 1938, complaining of pain in the left elbow and fore arm of six weeks' duration.

*Family History*—The patient's father, mother, six brothers, and three sisters were well.

*Past History*—The patient's general health had been good. He had had measles and pertussis in childhood and had had three attacks of influenza since 1918. Four years prior to the onset of the present illness he had had a chronic cough which lasted for several months. There was no hemoptysis, chest pain, or fever during this illness.

*Present Illness*—Eleven weeks before admission to the hospital, the patient noticed a small area of tenderness over the left eleventh rib which became increasingly painful. After three weeks a small swelling appeared which was incised by his physician with the evacuation of a small amount of sterile pus. The exposed rib was curetted and the wound has remained as an indolent cavity. Six weeks before hospitalization a swollen, tender spot developed over the left ulna just distal to the elbow joint. This swelling increased in size for about ten days and the patient noticed that movement of the elbow caused pain. Ten days before he entered the hospital this area was incised with evacuation of some necrotic bone. The pus from this wound was reported also as showing no growth of pyogenic organisms. Both wounds continued to drain and the elbow has remained painful.

*Physical Examination*—The patient was a 30 year old, undernourished white farmer, with normal temperature, pulse, and respirations. There were no abnormalities except for the two areas described. Over the left eleventh rib there was a cavity, 6 by 3 cm. in size, lined by indolent granulation tissue. The rib was not exposed at the bottom of the wound. The left elbow was markedly swollen.

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and any motion of the joint caused pain. Over the proximal end of the ulna, there was an incision 6 cm. in length which was lined with necrotic tissue and drained bloody pus.

*Accessory Clinical Findings.*—Hgb., 98 per cent; R.B.C., 4,480,000; W.B.C., 10,300. Differential: P.M.N. 86 per cent; L.L., 3 per cent; S.L., 8 per cent; E., 1 per cent, M., 2 per cent. Urine: acid, specific gravity, 1.023; albumin, negative; sugar, negative; microscopic examination showed only an occasional W.B.C.; Wassermann, negative; stool, negative. Blood Chemistry: N.P.N., 36; Ca, 8.6; P, 3.2; refractive index, 1.350.

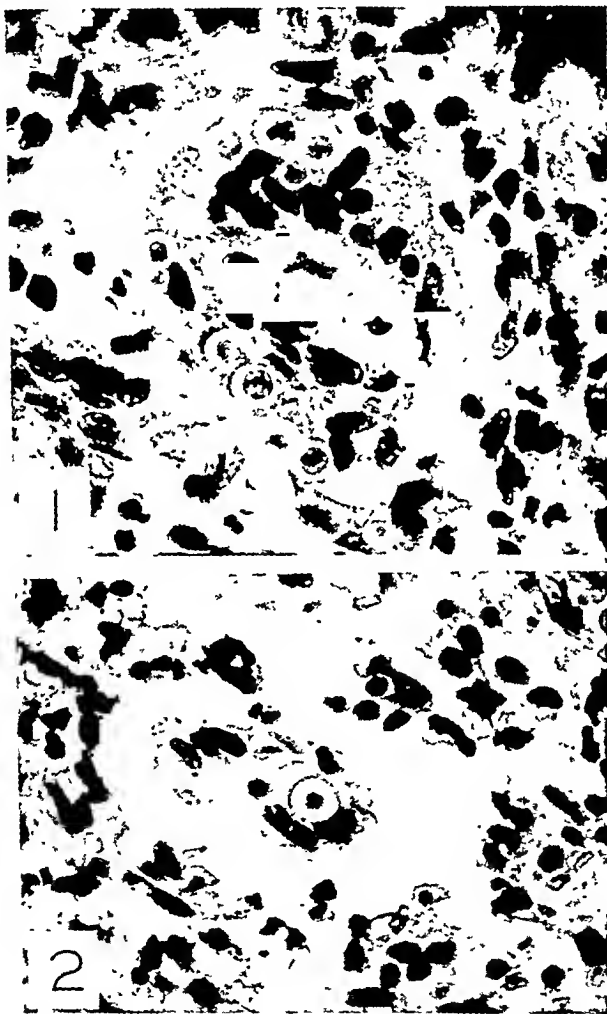


Fig. 2.—1, Biopsy section of skin from another case showing the usual appearance of *Blastomyces dermatitidis*; 2, Biopsy section of skin from present case to illustrate the difference in size of the double-contoured wall. For comparison, each of these sections was cut from blocks, mounted, and stained under identical conditions.

Roentgenograms showed a destructive process in the left eleventh rib, in the posterior axillary line, and in the left olecranon (Fig. 1, 1). The findings in both sites suggested osteomyelitis. Fluoroscopy and films of the chest showed a slight increase in the peribronchial markings bilaterally and a slight thickening of the pleura at the left apex.

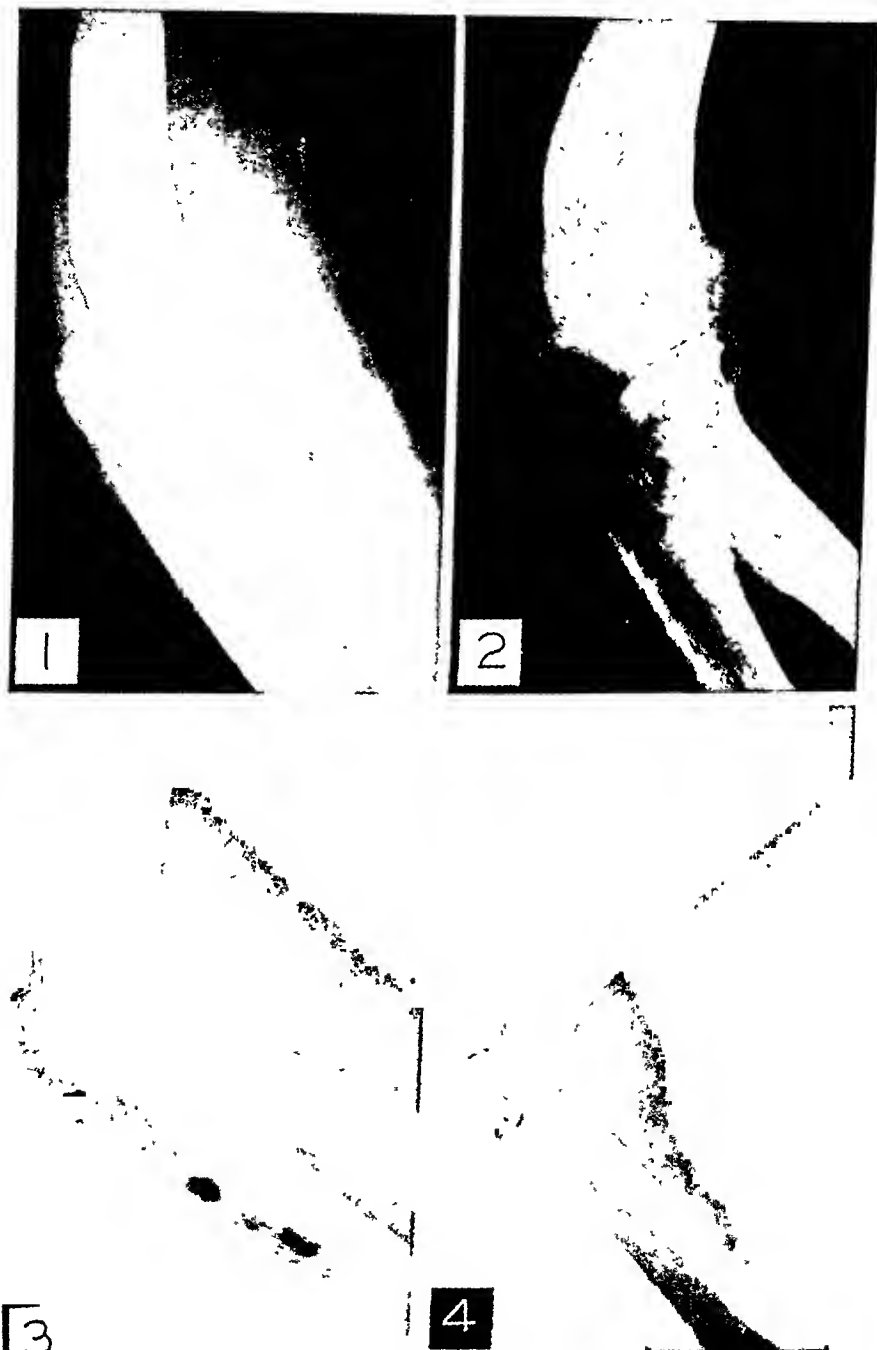


Fig. 1.—1, Roentgenologic appearance of elbow lesion on Aug. 29, 1933, before iodide therapy was begun; 2, appearance of bone lesion on Oct. 4, 1935; 3, appearance of bone lesion at time of discharge, May 1, 1939; 4, appearance of elbow lesion on return visit to the hospital, Aug. 11, 1940.



ing the following two weeks the patient gained 1.65 kg. in weight. An x ray on Oct 4, 1938 (Fig. 2, 2), showed that bone destruction had increased considerably under iodide therapy.

At this time amputation of the left arm was considered, but the patient demurred and he received 1,200 r. units of deep x ray therapy from Oct 20 to 25. The elbow lesion failed to improve clinically, but there was no evidence of a spread of the infection. The low grade fever slowly subsided as did the white count, which had been elevated following the serum injections (Fig 3). It was felt that the introduction of maggots might remove some of the necrotic tissue and increase drainage and these were introduced on Nov 9 and at intervals until Nov 23. During this time considerable healing of the bone was demonstrated by x ray. There were several bouts of fever during this treatment. Three weeks after maggots were first introduced, the patient developed multiple furuncles, hemolytic *Staphylococcus aureus* bacteremia, and a severe upper respiratory infection. Potassium iodide was discontinued Dec. 29. He was severely ill for three months, necessitating surgical treatment for the abscesses, several courses of sulfamidate and sulfapyridine, staphylococcus antitoxin, nicotinic acid, thiamin chloride, liver, and transfusions. Repeated examinations of the elbow lesion and of numerous abscesses and the sputum failed to demonstrate *Blastomyces*, and it was apparent that the fungus infection had been brought under control before the onset of the severe bacteremic infection with *Staphylococcus aureus*.

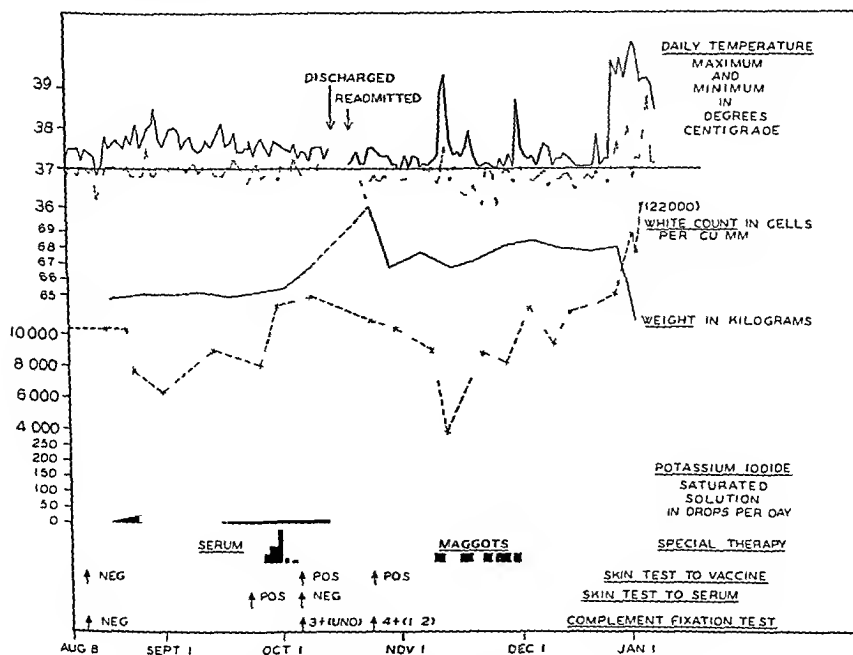


Fig 3—Chart illustrating the patient's course in the hospital

Following the injections of anti *Blastomyces* serum, there was a complete reversal of the immunologic picture. On Oct 5, 1938, the Foshay test was repeated and the results showed no increase in reaction to the anti *Blastomyces* serum as compared with the normal rabbit serum control. A skin test on Oct. 5 to a filtrate of *Blastomyces* gave a markedly positive reaction within twenty four hours, but the area of erythema had completely disappeared within forty eight hours. This

*Bacteriologic Studies.*—*Staphylococcus aureus* was grown from the rib lesion, but cultures for bacteria from the elbow region showed no growth. Cultures for tubercle bacilli were negative. There was no reaction to the intracutaneous injection of old tuberculin diluted 1:10,000.

*Mycologic Studies.*—Budding fungi were found in direct smear and in sections of material obtained by biopsy. The appearance of these organisms differed somewhat from the usual *Blastomyces dermatitidis* in that the double-contoured peripheral membrane of the fungus cells seemed much wider than usual (Fig. 2, 1 and 2). Although there was the definite impression that the organisms were true *Blastomyces*, several observers suggested that the fungus might prove to be a *Cryptococcus*. However, cultures of the fungus from this case on Sabouraud's medium at room temperature and on blood agar at 37° C. showed no essential differences from the usual *Blastomyces* isolated from cases of American blastomycosis.<sup>1</sup> There was also no detectable difference antigenically between this strain and other strains of *Blastomyces* when tested for combining capacity with an anti-*Blastomyces* rabbit serum.

*Course in the Hospital.*—The wounds were everted the day after admission. The cavity in the ulna was found to extend into the elbow joint, but the eleventh rib at operation was covered by a compact layer of granulation tissue.

Skin tests to a heat-killed vaccine and three fractions of *Blastomyces dermatitidis* were done on Aug. 12, 1938, four days after admission. No reaction was obtained with any of these substances. In view of the negative skin test to *Blastomyces dermatitidis* and the questionable diagnosis of cryptococcosis, the patient was injected intracutaneously with 0.1 c.c. of heat-killed vaccines prepared from three strains of pathogenic cryptococci. None of these was positive. Since the patient exhibited no signs of hypersensitivity to the fungus, potassium iodide was given by mouth, starting with three drops t.i.d. and increasing the dose at a rate of three drops per day. He was given, also, a high caloric, high vitamin diet. The wounds were treated with warm saline fomentations and the lesions cauterized on several occasions. Under this therapy the rib area improved, but the bone lesion in the elbow grew worse. By Sept. 23, 1938, forty-six days after admission, his iodide dosage had reached 114 drops per day, but he had gained only 0.35 kg. in spite of his enhanced diet. Except for a temperature of 38.5° C. on one occasion, he had only a low-grade fever. His white count varied between 6,350 and 10,450 (Fig. 3).

After six weeks' observation it was obvious that a more radical form of treatment was necessary to save the patient's arm. On Sept. 29, 1938, 0.1 c.c. of undiluted anti-*Blastomyces* rabbit serum was injected intracutaneously. Normal rabbit serum was used as a control. The anti-*Blastomyces* rabbit serum caused, within fifteen minutes, an edematous area 12 by 19 mm. surrounded by a zone of erythema 46 by 70 mm. During the same interval of time the control serum produced a raised area only 11 by 12 mm. and there was no erythema. This test is similar to that described by Foshay<sup>2</sup> except that 0.1 c.c. of undiluted serum was used instead of 0.04 c.c. of a 1:10 dilution as recommended by him.

Several subcutaneous injections of small doses of rabbit serum were given, the patient receiving 0.25 c.c. on Sept. 27, 0.5 c.c. on Sept. 28 and 29, and 1 c.c. on Sept. 30. The last dose which was injected into the left upper arm midway between the elbow and shoulder resulted in an intense local reaction which was greatest around the elbow. There was some erythema and swelling as high as 5 cm. above the site of injection, but the whole region of the elbow was greatly swollen and extended well down into the forearm. Because of the severity of the reaction, the dosage was cut to 0.1 c.c. on Oct. 2 and 0.05 c.c. on Oct. 4. There was no febrile reaction following the serum injections, but the white count rose to 12,000. Dur-

impressed by the morphologic appearance of the fungus in the lesion that they considered the organism to be a new species, *Endomyces capsulatus*. Cultural studies of this strain of *E. capsulatus* by Benham<sup>6</sup> and in this laboratory<sup>1</sup> have shown no essential differences from the usual strains of *Blastomyces dermatitidis* isolated from numerous cases of American blastomycosis.

The positive Foshay test further suggests that the fungus was producing some antigenic substance which may have masked or prevented the development of a skin reaction to the intracutaneous injection of dead organisms or filtrates of the organism. This substance presumably inhibited also the demonstration of antibodies in the serum of the patient. The severe local reaction around the elbow following the injection of 1.0 c.c. of anti-Blastomyces rabbit serum emphasized that production of this hypothetical antigenic material was most intense in the area of infection. The apparent benefit following the injection of only 2.4 c.c. of serum, with a complete reversal of the immunologic picture, may be interpreted by assuming that this excess material was neutralized by the antibodies in the rabbit serum, allowing the host's cells, aided by iodides, to attack the invading fungi. The positive complement fixation reactions could not have been explained by the passive transfer of antibodies because of the small amount of serum injected. The observation that the test became more strongly positive three weeks later suggested that the patient previously had built up a certain degree of resistance to the fungus but that evidences of this resistance were masked by the local production of this soluble antigen. This substance may have prevented local healing of the lesion and caused the reversal of the usual findings of hypersensitivity to the fungus and the presence of serum antibodies.

The role of hypersensitivity to bacteria or bacterial products in infections is debatable. It seems that a certain amount of allergy is desirable in localizing an infection but that too great a degree of allergy is harmful because of the severity of the reaction following a spread of the infection or the liberation of bacterial products. In none of our previous cases was desensitization with *Blastomyces* vaccine complete and in this case the mild degree of allergy which developed after serum treatment did not seem to be sufficient to warrant discontinuation of iodides.

The role of maggots in the ultimate cure of this patient was felt to be due entirely to their action in removing necrotic tissue and maintaining of open sinuses for drainage. The possibility that maggots could have had any direct fungicidal effect was not investigated.

A third factor that must be considered is the effect of the severe staphylococcal infection. It has been shown experimentally by Baker<sup>7</sup> that mice infected intraperitoneally have less marked lesions if the peritonitis is complicated by bacterial infection. It is difficult, however, to believe that the presence of bacterial infection in this patient played a

same type of reaction is obtained in allergic patients when tested with a purified carbohydrate fraction of the fungus.<sup>3</sup> The patient's serum, previously negative for complement fixing antibodies, gave a weakly positive reaction on Oct. 6 (3+ in undiluted serum) and a stronger reaction on Oct. 21 (4+ in 1:2 dilution of serum). The complement fixation test was negative at the time of discharge on April 3, 1939, but a skin test to the same filtrate again resulted in a positive twenty-four-hour reaction. The extent of reaction was less than that previously found.

The patient was discharged from the hospital on April 4, 1939, with the wound on the elbow completely healed. An x-ray of the bone on May 1, 1939, showed considerable filling in of the bone cavity (Fig. 1, 3). He was last seen on Aug. 14, 1940, and had no more symptoms. He had gained approximately 15 kg. in weight and had complete range of motion of his elbow. An x-ray at this time (Fig. 1, 4) showed healing of the bone except for a fracture line across the olecranon. It was felt that this line of decreased density represented healing of the cavity with fibrous tissue rather than a true fracture, since the patient had complete function of the joint and there were no physical signs or symptoms suggestive of fracture.

#### DISCUSSION

It is very difficult to evaluate the effects of specific forms of therapy in a disease such as blastomycosis because the limited number of patients seen by any individual or clinic makes statistical analysis of no value. Furthermore, like tuberculosis, each case presents a different problem and must be treated individually.

In this patient evaluation of treatment is especially difficult, since he received iodides, deep x-ray therapy and antiblastomycotic rabbit serum in addition to surgical procedures, such as curettement, cauterization, and application of maggots into the wound. The results of treatment in this patient, as compared with our experiences with other patients with this disease,<sup>4</sup> have suggested to us certain possibilities which are outlined below.

Iodides have been shown by us<sup>4</sup> to be potentially harmful to patients who have developed a high degree of allergy to the infecting fungus. This patient, with no evidences of hypersensitivity to the fungus, theoretically should have responded well to the drug. However, during the six-week period of iodide administration he continued to have low-grade fever, failed to gain significantly in weight, and the local lesion in his elbow became worse. The appearance of the fungus in smears suggested either a different form of the fungus or a peculiar reaction of the host cells to the fungus. This has its counterpart in other fungus infections, actinomycosis in particular, in which the club-shaped swellings of the mycelia in the periphery of the sulfur granules are thought to represent the results of an interaction between the host and the parasite, since these swellings are rarely observed in culture. It is not certain whether or not *Blastomyces dermatitidis*, under certain conditions, may form a capsule in animal tissues or whether the capsular appearance represents only an exaggeration of the usual thick-walled membrane. However, in a case reported by Rewbridge, Dodge, and Ayers,<sup>5</sup> the authors were so

impressed by the morphologic appearance of the fungus in the lesion that they considered the organism to be a new species, *Endomyces capsulatus*. Cultural studies of this strain of *E. capsulatus* by Benham<sup>6</sup> and in this laboratory<sup>1</sup> have shown no essential differences from the usual strains of *Blastomyces dermatitidis* isolated from numerous cases of American blastomycosis.

The positive Foshay test further suggests that the fungus was producing some antigenic substance which may have masked or prevented the development of a skin reaction to the intracutaneous injection of dead organisms or filtrates of the organism. This substance presumably inhibited also the demonstration of antibodies in the serum of the patient. The severe local reaction around the elbow following the injection of 1.0 c.c. of anti-Blastomyces rabbit serum emphasized that production of this hypothetical antigenic material was most intense in the area of infection. The apparent benefit following the injection of only 2.4 c.c. of serum, with a complete reversal of the immunologic picture, may be interpreted by assuming that this excess material was neutralized by the antibodies in the rabbit serum, allowing the host's cells, aided by iodides, to attack the invading fungi. The positive complement fixation reactions could not have been explained by the passive transfer of antibodies because of the small amount of serum injected. The observation that the test became more strongly positive three weeks later suggested that the patient previously had built up a certain degree of resistance to the fungus but that evidences of this resistance were masked by the local production of this soluble antigen. This substance may have prevented local healing of the lesion and caused the reversal of the usual findings of hypersensitivity to the fungus and the presence of serum antibodies.

The role of hypersensitivity to bacteria or bacterial products in infections is debatable. It seems that a certain amount of allergy is desirable in localizing an infection but that too great a degree of allergy is harmful because of the severity of the reaction following a spread of the infection or the liberation of bacterial products. In none of our previous cases was desensitization with *Blastomyces* vaccine complete and in this case the mild degree of allergy which developed after serum treatment did not seem to be sufficient to warrant discontinuation of iodides.

The role of maggots in the ultimate cure of this patient was felt to be due entirely to their action in removing necrotic tissue and maintaining of open sinuses for drainage. The possibility that maggots could have had any direct fungicidal effect was not investigated.

A third factor that must be considered is the effect of the severe staphylococcal infection. It has been shown experimentally by Baker<sup>7</sup> that mice infected intraperitoneally have less marked lesions if the peritonitis is complicated by bacterial infection. It is difficult, however, to believe that the presence of bacterial infection in this patient played a

part in controlling the fungus infection because improvement in the latter occurred before the appearance of abscesses and bacteremia.

#### SUMMARY

An unusual case of blastomycosis of bone is presented.

After failure to obtain improvement with iodides, this treatment was supplemented by subcutaneous injections of small amounts of immune serum and the introduction of maggots into the local lesion.

The possible effects of these two additional agents in bringing about the ultimate cure of the patient are discussed.

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## LOCAL SULFANILAMIDE THERAPY IN SURGICAL INFECTIONS

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THE introduction of the sulfonamides has changed entirely the mode of treatment for many diseases. The adaptation of these new drugs to the therapy of surgical infections has been relatively slow due to the comparatively poor results obtained by their oral and parenteral administration in walled-off pyogenic lesions.

Meleney and Harvey,<sup>1</sup> in 1939, reported a series of 40 chronic undermining ulcers infected with hemolytic streptococci treated with local application of zinc peroxide and the oral administration of sulfanilamide. In the cases with an associated acute cellulitis and lymphangitis they obtained good results. In the more chronic cases, in which there were considerable necrosis, undrained abscesses, and locally decreased blood supply, the sulfanilamide was without effect. Bricker and Graham,<sup>2</sup> also in 1939, found that the oral administration of sulfanilamide retarded the healing processes of clean incised wounds of dogs' stomach. These experiments were later repeated by Taffell and Harvey,<sup>3</sup> who did not demonstrate any abnormality of healing. Key and Burford<sup>4</sup> have stated that they found no inhibition of healing in experimental fractures in rabbits after the local instillation of sulfanilamide at the site of fracture. Jensen, Johnsrud, and Nelson<sup>5</sup> reported 39 cases of compound fractures treated by careful débridement and the local implantation of powdered sulfanilamide. These wounds were then closed. All healed by primary union. Ninety-four similar cases treated in the same manner without sulfanilamide had a total of 29 infections. Campbell and Smith,<sup>7</sup> reporting 54 cases of compound fractures treated with local application of sulfanilamide, did not feel that the incidence of infection was materially reduced in the acute cases. However, they found that the drug greatly reduced the incidence of post-operative infections in cases in which surgery was undertaken in the presence of chronic inflammation. Rapid control of secondary infection in chancreoids by the topical application of sulfanilamide powder was first described in 1938 by Fields and Weinstein.<sup>8</sup> Since the advent of the current war several papers have appeared in which the authors claim excellent results from the local use of sulfone drugs in contaminated and infected war wounds.<sup>9-11</sup> Levaditi<sup>12</sup> has reported rapid and effective sterilization of war wounds by the local application of sulfanilamide. Oral administration of the drug in such cases was ineffective.

Considerable material is now available on the bacteriostatic and bactericidal effects of sulfonamides in vitro against the common contaminants of surgical wounds.<sup>13-17</sup> Lawrence<sup>18, 19</sup> has investigated the comparative effects of the various sulfonamide drugs upon cultures of the colon-typhoid-dysentery group. Most of the investigators agree that the maximum bacteriostatic effect is obtained in an aerobic medium.<sup>20-22</sup> Lockwood<sup>23, 24</sup> has recently reported upon the mode of action of these drugs as applied to local bacteriostasis in infected lesions. He believes that they act locally by interfering with the nutritional requirements of certain bacteria, the effect being dependent upon the concentration of the drug and the amount of free peptone available from tissue necrosis. Whether this theory or the anticatalase theory<sup>25, 26</sup> is correct, the need of débridement of all necrotic tissue and the continued local concentration of the drug is paramount. Since 1936 Ravdin<sup>27</sup> has routinely given sulfanilamide parenterally and orally in all cases of acute appendicitis and appendical abscesses. He and his associates report a pronounced lowering of morbidity and mortality rates since initiating this routine. Recently the local intraperitoneal application of sulfanilamide powder to the region of the appendix has been described by Thompson, Brabson, and Walker.<sup>28</sup> In 204 cases of purulent or ruptured appendices they placed 12 Gm. of sterilized sulfanilamide powder into the peritoneal cavity and the muscle layers of the abdominal incision. No toxic effects or local devitalization of tissues was noticed.

During the past year we have treated over 300 infected wounds by the local implantation of sulfanilamide powder.<sup>29</sup> These cases include postoperative wound infections, many types of traumatic wounds, infected burns, compound fractures, leg ulcers, decubitus ulcers, localized abscesses, and carbuncles. The results obtained by this method have been so excellent that it has now largely supplanted all other forms of local treatment of infected wounds in our hospital. The chief advantages are its rapid, effective, and nonirritative action, the simplicity of the dressing care needed, and the comfort afforded the patient. It is also cheap and readily accessible. We have encountered some disadvantages with its use. Most of these disadvantages can be overcome if certain rules are followed. In this communication we wish to record the technique employed and the results obtained in the local treatment of infected wounds with sulfanilamide.

We have endeavored to determine the direct effect of sulfanilamide on the various organisms found in these pyogenic wounds. In a large series of cases smears and cultures were made before beginning the local treatment. At intervals during the period of treatment similar bacteriologic studies were repeated. Biopsies of the edges of the wounds were also taken in a group of 70 cases, showing sections of the tissues before treatment and during the process of healing. In this manner we have obtained a qualitative and, in a sense, a quantitative test of



the action of sulfanilamide upon the local tissue. In the great majority of our cases the smears and cultures showed a mixed flora of bacteria. Chief among these were streptococci, staphylococci, the *Bacillus coli* group, and diphtheroids. An important secondary invader in some cases was *Bacillus pyocyaneus*. After the preliminary bacteriologic and microbiologic studies were completed the wounds were treated by adequate drainage or débridement and the local implantation of sulfanilamide powder. The dose of sulfanilamide introduced was determined by the size of the lesion. A sufficient quantity was used to cover the wound surface completely and to fill all pockets. On the following day the smears and cultures were repeated. There was an immediate diminution in the number of organisms found in the smears and the colonies grown on plated cultures. All of the types of organisms found in these wounds were affected. In those cases in which a new supply of sulfanilamide was not introduced we found that there was usually a reactivation of the bacterial growth. If daily applications of sulfanilamide were made, however, the number of bacteria continued to decline until there was a practical sterilization of the wound. This usually required from five to eight days. Along with the reduction in number of bacteria there was a striking diminution in the amount of exudate. The necrotic odor of some of the wounds was immediately banished. This has been particularly noticeable in the cases of ruptured appendices where it had been necessary to drain the abscess. After the bacterial growth and exudate had been controlled we discontinued the sulfanilamide. In some of the cases the wounds remained clean and healing processes progressed steadily. In others we observed that there was a gradual resumption of the bacterial growth and a return of inflammation. We then resumed the daily instillation of the sulfanilamide. By continuing the application of the drug we maintained control of the infection, but another complication developed. In some cases the healing came to a complete standstill. The granulation tissue appeared dry, anemic, and indolent. As long as the concentrated drug was used the healing was retarded. Biopsies from the lesions at this stage showed very poor vascularization of the granulation tissue. Complete removal of the sulfanilamide was sometimes followed by more abundant granulations and resumption of wound healing. In some cases, however, the invading organisms again became active, and we were once more dealing with an infected wound. It seemed desirable to keep available in the wound some sulfanilamide, yet not enough to hinder healing. We then attempted to use a less concentrated form of the drug after the initial infection had been controlled. Aqueous solutions and oil suspensions proved inadequate,<sup>30</sup> and the incorporation of the drug into various inert ointments was not satisfactory. We then requested the National Drug Co. to prepare for us an ointment combining sulfanilamide and allantoin in a greasless base. According to Robinson<sup>31</sup> and others<sup>32, 33</sup>

allantoin produces a stimulating effect on indolent granulation tissues by increasing their vascularity. After several trials we found that a combination of sulfanilamide 10 per cent with allantoin 2 per cent in an absorbable glycerinated base did give remarkably good results. Within a few days following the substitution of the ointment in place of the concentrated powdered sulfanilamide the tissues became active and healthy in appearance and the infection remained under control. (Figs. 1, A, B, and C.) In a number of cases the same ointment was used without including allantoin in the formula. Although these wounds healed and lacked the indolent phase characteristic of full-strength sulfanilamide, the growth of granulation tissue was not as rapid or as freely bleeding as when allantoin was used.



Fig. 1A.—Biopsy specimen from necrotic infected ulcer. Low power ( $\times 260$ ). Note marked inflammatory reaction. Section taken before treatment.

From these studies we have now developed a more or less routine method of using sulfanilamide to prevent infections in contaminated open injuries and to control bacterial growth in grossly infected wounds. The first step is the proper preparation of the wound. In order for the drug to be effective it must come into direct contact with the invading organisms. The wounds must be adequately drained, necrotic tissue must be removed, and all surfaces of the wound made available for topical application of the powder. (Fig. 2 A-C.) When the field is thus prepared, a sufficient quantity of the concentrated sulfanilamide powder

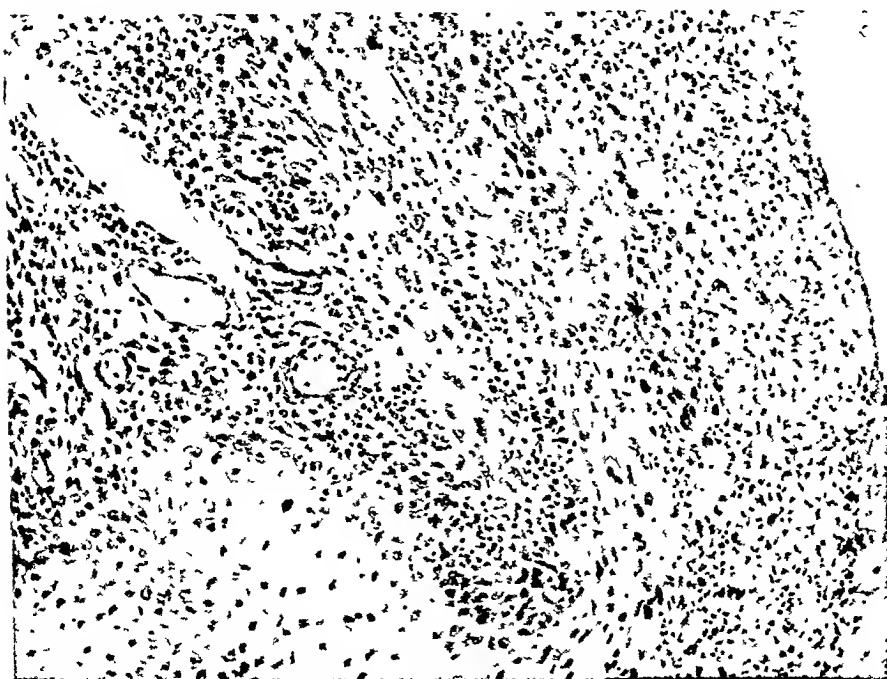


Fig. 1B.—Biopsy specimen taken from case shown in Fig. 1A after ten days' treatment with sulfanilamide locally. Low power (X260) There is a diminution in inflammatory reaction, but scant vascularization.

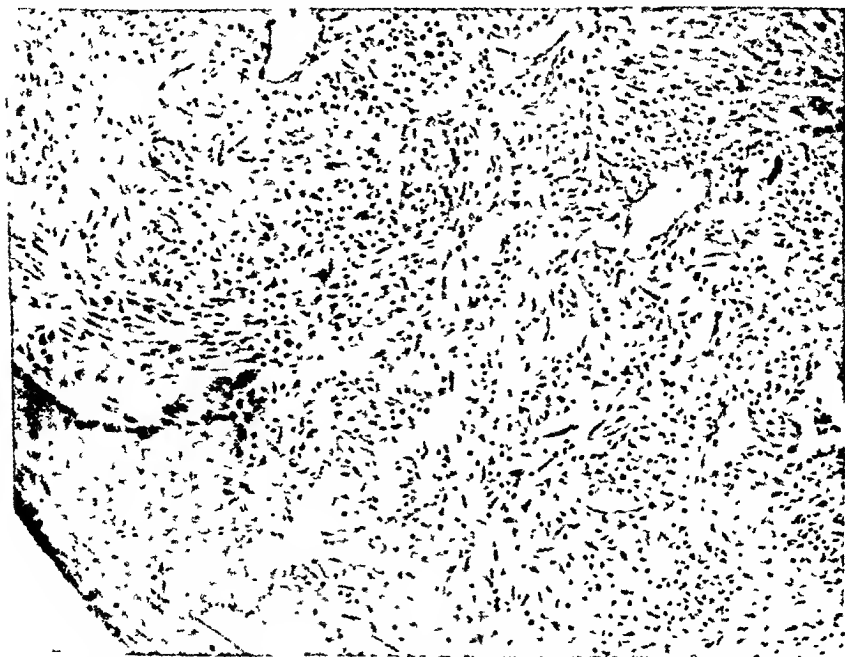


Fig. 1C.—Biopsy specimen of case shown in Figs 1A and B ten days later after substituting sulfanilamide-allantoin ointment. Low power (X260) Note control of infection and abundant vascularization

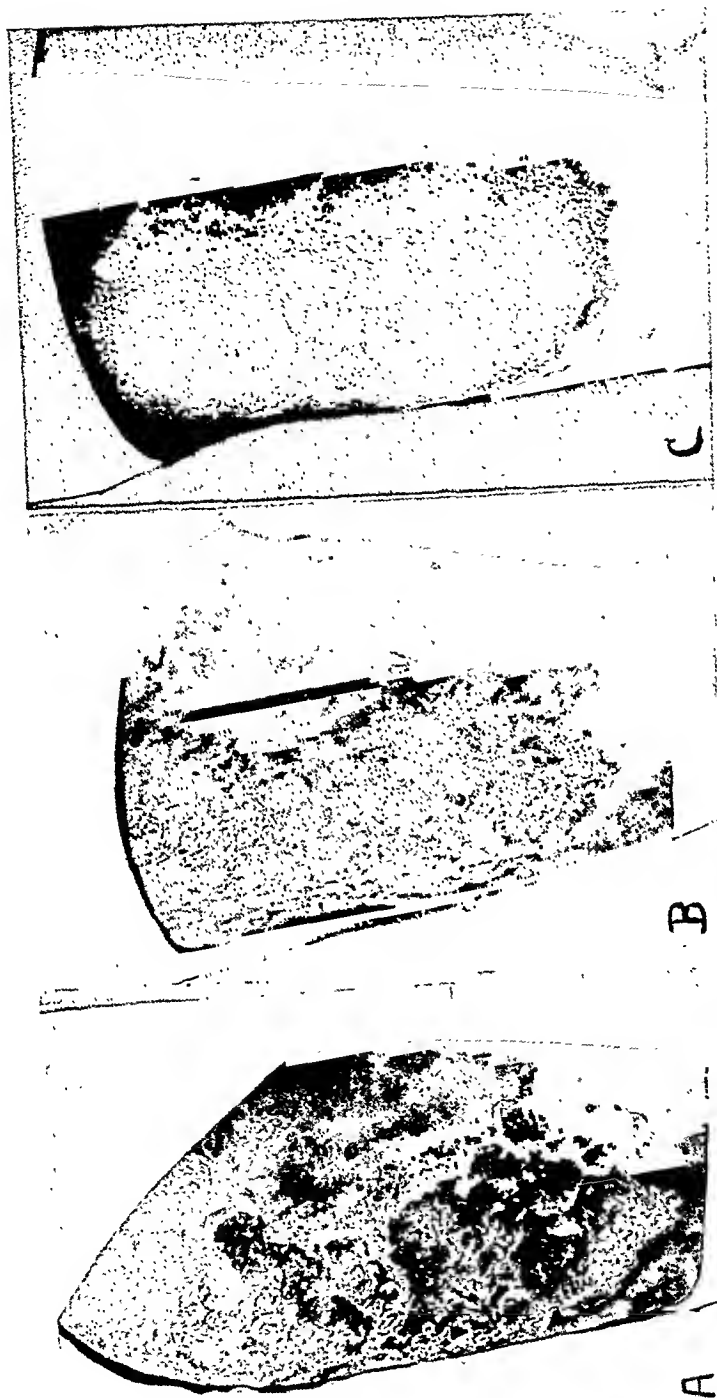


Fig. 2.—A. Photograph of infected burn of thigh showing crusting with exudate. B. Same case after débridement and control of bleeding. The field is thus made ready for the reception of the sulfanilamide powder. C. Same case showing entire lesion covered with sulfanilamide powder.

is placed upon the wound to cover the surface entirely and a dry dressing is applied. (We have not found it necessary to measure the dosage. In most cases 5 to 10 Gm. has been applied daily until the infection was controlled.) As soon as bacterial growth and exudate has diminished and the signs of inflammation have subsided, the powdered sulfanilamide is discontinued and is replaced by daily dressings of the sulfanilamide-allantoin ointment. The ointment is applied as a thin layer over the entire lesion, which is then covered with a dry gauze dressing. This type of treatment is continued daily until the wound is healed or until the field is covered with a skin graft.

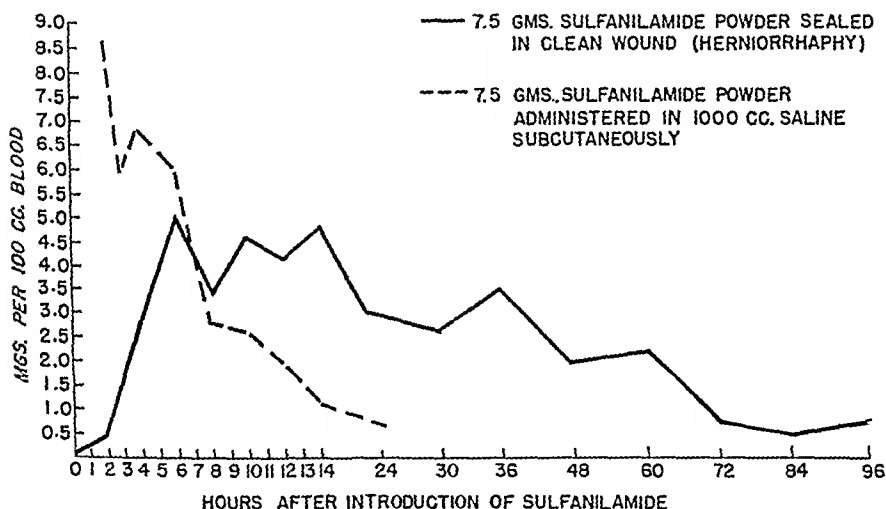


Fig. 3.—Chart showing comparison of blood sulfanilamide levels when 7.5 Gm. of sulfanilamide powder is sealed in a clean wound and the same dose given subcutaneously in 1,000 c.c. of normal saline solution. Note the delayed absorption of the drug from the sealed wound.

The method of treating infected wounds as outlined above has now largely replaced all other methods in our wards and in our out-patient clinics. The simplicity of the method is of great practical value. The disadvantages of wet dressings and irrigation techniques are overcome. Special mention should be made of its merits in preparing wide areas for skin grafts. Our percentage of graft "takes" has been greatly increased and the period of preparation has been materially reduced.

We have not attempted to measure the total dosage of sulfanilamide used in any particular wound. In many cases 5 to 10 Gm. of the powder was used daily for many days without any systemic symptoms. The blood concentration of the drug has been far less than that generally accepted as a "therapeutic level" for oral or parenteral administration in systemic diseases. In studying the rate of absorption from various types and sizes of wounds, we have found wide variations in the blood levels.

A single dose of 7.5 Gm. closed in a clean operative wound usually shows a rapid rise, approaching the level obtained by giving the same dose by mouth. There is then a gradual decline in the rate of absorption, but traces of the drug may be found in the blood for several days. (Fig. 3.) The same dose instilled in an open wound shows a much lower blood concentration (Fig. 4). In none of our cases has there been any evidence of a systemic toxic reaction. The peculiar cyanosis so frequently seen

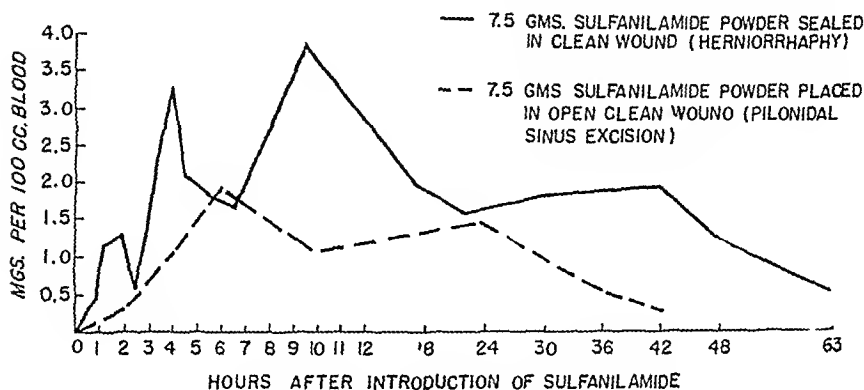


Fig. 4.—Chart showing comparison of blood sulfanilamide levels from 7.5 Gm. of sulfanilamide powder when sealed in clean wound and when implanted in open wound

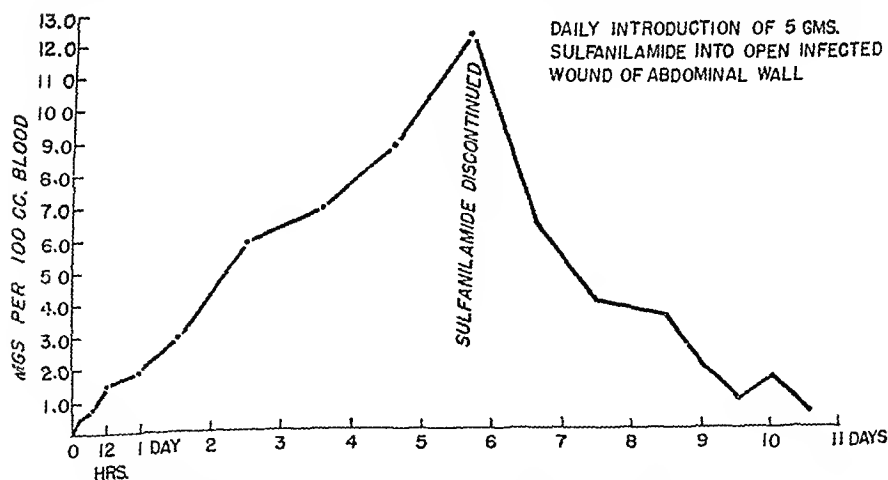


Fig. 5.—Chart showing accumulative rises of sulfanilamide blood concentration when 5 Gm. of the drug is applied daily in open infected wound

when the drug is given by mouth or parenterally has not been observed in the locally treated cases. We have, however, observed a cumulative rise of the blood sulfanilamide level in certain cases in which large daily doses were used over a long period of time (Fig. 5). A recent article by Hooker and Lam<sup>34</sup> indicates that there may be a very rapid absorption from the extensive surfaces of acute burns. This possibility should be

borne in mind when using the concentrated powder over a prolonged course of treatment.

#### SUMMARY

Sulfanilamide powder rapidly controls bacterial growth in infected surgical wounds when it is placed directly into the lesion. The wound must be prepared by adequate drainage or débridement for the reception of the drug. The local action of sulfanilamide on the bacteria depends upon its molecular concentration in the wound. Therefore, it must be applied in sufficient quantity and must come into direct contact with the invading organisms. The growth of all the pyogenic organisms commonly found in infected wounds is apparently inhibited by sulfanilamide. Chief among these are streptococci, staphylococci, and the colon group. The common secondary invader, *B. pyocyaneus*, is promptly destroyed by local application of the drug. Prolonged use of concentrated sulfanilamide may retard healing. This probably results from inhibition of cellular growth and the retardation of vascularization of the granulation tissue. The substitution of sulfanilamide-allantoin ointment for the pure powder allows a prompt resumption of the normal healing process and at the same time maintains a clean wound.

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## CHANGES PRODUCED BY SYMPATHECTOMY IN THE ELECTRICAL RESISTANCE OF THE SKIN

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**S**URGICAL treatment of circulatory disturbances of the skin has been handicapped (a) by a lack of knowledge regarding the distribution of the sympathetic nerves to the skin and (b) by the lack of an adequate method of demonstrating the skin areas affected by sympathectomy. These shortcomings have been overcome, at least in large part, by the use of the so-called electrical skin resistance method.

This method depends on the changes produced by sympathectomy on the resistance offered by the skin to the passage of a small direct electrical current. Since various factors influence skin resistance, a brief review will be given at this point of some of the essential underlying neurologic and physiologic principles, as well as of the origin of our interest in problems concerned with the electrical resistance of the skin.

Incidental to early studies on the galvanic skin reflex in psychiatric patients, it was found that some patients had a very high skin resistance which reached levels of 1,000,000 to 3,000,000 ohms, while others had a resistance of only a few thousand ohms. A separate investigation was then undertaken to determine whether these resistance levels could be correlated with the different types of psychoses and at the same time to learn more about the physiologic and neurologic factors underlying the resistance offered by the body to the passage of a small direct current.

For these experiments the following technique was used: Four solid disks of zinc were used as electrodes. These were placed against the palmar and dorsal surfaces of the two hands, using a paste made of kaolin and saturated zinc sulfate solution to provide a contact between the electrodes and the skin. Any pair of these electrodes could be connected to a galvanometer which measured the resistance offered to the passage of an imperceptible current.<sup>1, 2</sup>

From these studies the following information was obtained: (a) The resistance offered by the body to the passage of a small direct current is localized almost entirely in the skin. Punctures made through the skin underneath the electrodes reduced the resistance instantaneously from any level, however high, to only a few hundred ohms. Similarly, abrasions of the skin greatly reduce the resistance. (b) The resistance of the skin varies to a certain extent with its anatomical structure, chiefly with its supply of sweat glands. Thus, the porous areas of the palmar surfaces of the hands usually have a lower resistance than the skin on the relatively nonporous areas of the dorsal surfaces. Thus, for nine normal individuals the palmar resistance averaged 77.100 ohms; the dorsal

resistance, 290,310 ohms.<sup>4</sup> (c) The resistance on both surfaces depends largely on the sweat gland activity, being high when the sweat glands are inactive (that is, when the skin is dry) and low when the sweat glands are active (that is, when the skin is moist). (d) The resistance readings on the porous and nonporous areas may vary independently of one another. (e) Skin resistance varies with normal and pathologic sleep and sleep induced by hypnotics, in general, being high during sleep and low during the waking state.<sup>2, 4-6</sup>

It also was found that skin resistance is controlled to a large extent through the autonomic nervous system. In our first experiments, applying to monkeys essentially the same technique used on human beings, it was found that section of the entire nervous supply to the extremities (in the upper extremities the brachial plexus, in the lower extremities the sciatic and femoral nerves) greatly increased the resistance, especially on the palmar surfaces of the hands and feet. In some animals the palmar resistance increased from 20,000 or 30,000 ohms to 5,000,000 or 10,000,000 ohms, at which levels it remained permanently. The section of these trunks included sympathetic and somatic nerves. Further experiments were undertaken to sever these two types of nerves separately. Section inside of the cord of all of the anterior and posterior roots to the foreleg, which removed all of the somatic supply but did not interfere with the sympathetic nerve supply, had no effect on the skin resistance. Removal of the sympathetic chain, however, produced as great an initial increase in skin resistance as section of the entire nerve. After several months the resistance decreased to a permanent level of 1,000,000 to 2,000,000 ohms, which was still far above the preoperative level. It was thus proved that skin resistance depends primarily on the sympathetic nervous system.<sup>2, 7</sup>

This same technique has been used to study injury and repair within the sympathetic nervous system.<sup>8-10</sup> In experiments on cats it was found that a preganglionic section of the white rami to the stellate and first thoracic ganglion produced a large but temporary increase in skin resistance on the central pads of the forefeet. The resistance, which returned to its preoperative level in twenty to sixty days, closely paralleled the return of normal sweat gland activity. Thus, skin resistance gave a good measurement of the regeneration of the preganglionic fibers. Postganglionic sympathectomy through section of the gray rami from the stellate ganglion and the first thoracic ganglion produced an even greater increase in skin resistance on the larger central pads, but the resistance did not return to its preganglionic level. Even after ten months the resistance in some of the cats averaged over 3,000,000 ohms. The considerably higher levels of skin resistance produced by postganglionic as compared to preganglionic sympathectomy demonstrated that the ganglia have at least a certain degree of independent control over the peripheral mechanisms. This independence of function of the sympathetic ganglia may be the basis of the difference in the responses

of the vascular system to adrenalin after preganglionectomy and postganglionectomy reported by White and co-workers,<sup>11-13</sup> Grant,<sup>14</sup> and Ascroft.<sup>15</sup>

The dependence of skin resistance on the sympathetic nervous system was further brought out by experiments made on cats and monkeys in which the spinal cord was sectioned at various levels, above and below the thoracolumbar outflow of the sympathetic nerves. Complete transections made at  $C_7$  and  $C_8$  (that is, above the thoracic outflow) produced a large increase in the palmar resistance on both the fore- and hindfeet; complete transection at  $T_7$  (that is, below the thoracic outflow to the foreleg) had no effect on the forefoot but produced a large increase in the resistance of the hindfeet; complete transection at  $L_3$  (that is, below the outflow to both fore- and hindfeet) which completely paralyzes the hindlegs, had no effect on the skin resistance of either the fore- or hindfeet.<sup>16</sup> Further, the resistance closely followed the condition of the spinal cord. During the period of shock, when the legs were completely paralyzed, the resistance remained high; gradually, as the spinal reflexes began to appear, the resistance decreased. However, the return of the spinal reflexes preceded by many days the return of the normal function of the sweat glands, as shown by the return of the skin resistance to its preoperative level.

This method was applied in 1927 to the study of a patient in whom a tumor had completely blocked off the sympathetic chain on the right side of the neck and all of the sympathetic connections to the right arm and hand. In this patient the resistance of the palmar and dorsal surfaces was considerably higher on the side of the lesion. In the sweat bath the right hand remained dry.<sup>17</sup> In 1937 observations were made on the palmar and dorsal resistance changes of the hands of eight patients with cervical sympathectomies and of two patients with lumbar sympathectomies. They all showed respectively a greatly increased resistance on the palmar and dorsal surfaces of the hands and on the plantar and dorsal surfaces of the feet.<sup>18</sup> Smithwick<sup>19</sup> has recently reported that sympathectomy increases skin resistance.

#### METHODS

The method which has now been devised makes it possible to determine changes produced by sympathectomy on the electrical resistance of the skin not only on the palmar and dorsal surfaces of the hands but also on all other parts of the body (see Fig. 1). A zinc sheet disk,  $\frac{1}{2}$  inch in diameter, was attached to the lobe of one ear with an earring clip directly over a skin puncture made with a hypodermic needle. A paste made of kaolin and saturated zinc sulfate solution made contact between the electrode and the skin. The puncture through the skin reduced the resistance under this electrode to a negligibly low level. The other electrode consisted of a zinc sheet, about  $\frac{1}{4}$  inch in diameter, attached at right angles to an insulated handle, about 3 inches long. By the

resistance, 290,310 ohms.<sup>3</sup> (c) The resistance on both surfaces depends largely on the sweat gland activity, being high when the sweat glands are inactive (that is, when the skin is dry) and low when the sweat glands are active (that is, when the skin is moist). (d) The resistance readings on the porous and nonporous areas may vary independently of one another. (e) Skin resistance varies with normal and pathologic sleep and sleep induced by hypnotics, in general, being high during sleep and low during the waking state.<sup>2, 4-6</sup>

It also was found that skin resistance is controlled to a large extent through the autonomic nervous system. In our first experiments, applying to monkeys essentially the same technique used on human beings, it was found that section of the entire nervous supply to the extremities (in the upper extremities the brachial plexus, in the lower extremities the sciatic and femoral nerves) greatly increased the resistance, especially on the palmar surfaces of the hands and feet. In some animals the palmar resistance increased from 20,000 or 30,000 ohms to 5,000,000 or 10,000,000 ohms, at which levels it remained permanently. The section of these trunks included sympathetic and somatic nerves. Further experiments were undertaken to sever these two types of nerves separately. Section inside of the cord of all of the anterior and posterior roots to the foreleg, which removed all of the somatic supply but did not interfere with the sympathetic nerve supply, had no effect on the skin resistance. Removal of the sympathetic chain, however, produced as great an initial increase in skin resistance as section of the entire nerve. After several months the resistance decreased to a permanent level of 1,000,000 to 2,000,000 ohms, which was still far above the preoperative level. It was thus proved that skin resistance depends primarily on the sympathetic nervous system.<sup>2, 7</sup>

This same technique has been used to study injury and repair within the sympathetic nervous system.<sup>8-10</sup> In experiments on cats it was found that a preganglionic section of the white rami to the stellate and first thoracic ganglion produced a large but temporary increase in skin resistance on the central pads of the forefeet. The resistance, which returned to its preoperative level in twenty to sixty days, closely paralleled the return of normal sweat gland activity. Thus, skin resistance gave a good measurement of the regeneration of the preganglionic fibers. Postganglionic sympathectomy through section of the gray rami from the stellate ganglion and the first thoracic ganglion produced an even greater increase in skin resistance on the larger central pads, but the resistance did not return to its preganglionic level. Even after ten months the resistance in some of the cats averaged over 3,000,000 ohms. The considerably higher levels of skin resistance produced by postganglionic as compared to preganglionic sympathectomy demonstrated that the ganglia have at least a certain degree of independent control over the peripheral mechanisms. This independence of function of the sympathetic ganglia may be the basis of the difference in the responses

of the vascular system to adrenalin after preganglionectomy and post-ganglionectomy reported by White and co-workers,<sup>11-13</sup> Grant,<sup>14</sup> and Ascroft.<sup>15</sup>

The dependence of skin resistance on the sympathetic nervous system was further brought out by experiments made on cats and monkeys in which the spinal cord was sectioned at various levels, above and below the thoracolumbar outflow of the sympathetic nerves. Complete transections made at  $C_7$  and  $C_8$  (that is, above the thoracic outflow) produced a large increase in the palmar resistance on both the fore- and hindfeet; complete transection at  $T_7$  (that is, below the thoracic outflow to the foreleg) had no effect on the forefeet but produced a large increase in the resistance of the hindfeet; complete transection at  $L_3$  (that is, below the outflow to both fore- and hindfeet) which completely paralyzes the hindlegs, had no effect on the skin resistance of either the fore- or hindfeet.<sup>16</sup> Further, the resistance closely followed the condition of the spinal cord. During the period of shock, when the legs were completely paralyzed, the resistance remained high; gradually, as the spinal reflexes began to appear, the resistance decreased. However, the return of the spinal reflexes preceded by many days the return of the normal function of the sweat glands, as shown by the return of the skin resistance to its preoperative level.

This method was applied in 1927 to the study of a patient in whom a tumor had completely blocked off the sympathetic chain on the right side of the neck and all of the sympathetic connections to the right arm and hand. In this patient the resistance of the palmar and dorsal surfaces was considerably higher on the side of the lesion. In the sweat bath the right hand remained dry.<sup>17</sup> In 1937 observations were made on the palmar and dorsal resistance changes of the hands of eight patients with cervical sympathectomies and of two patients with lumbar sympathectomies. They all showed respectively a greatly increased resistance on the palmar and dorsal surfaces of the hands and on the plantar and dorsal surfaces of the feet.<sup>18</sup> Smithwick<sup>19</sup> has recently reported that sympathectomy increases skin resistance.

#### METHODS

The method which has now been devised makes it possible to determine changes produced by sympathectomy on the electrical resistance of the skin not only on the palmar and dorsal surfaces of the hands but also on all other parts of the body (see Fig. 1). A zinc sheet disk,  $\frac{1}{2}$  inch in diameter, was attached to the lobe of one ear with an earring clip directly over a skin puncture made with a hypodermic needle. A paste made of kaolin and saturated zinc sulfate solution made contact between the electrode and the skin. The puncture through the skin reduced the resistance under this electrode to a negligibly low level. The other electrode consisted of a zinc sheet, about  $\frac{1}{4}$  inch in diameter, attached at right angles to an insulated handle, about 3 inches long. By the

handle this electrode could be held against the skin and could be moved freely from place to place. The use of this electrode represents one of the most important steps in this technique. In our former studies electrodes were fixed firmly to only four surfaces, the palms and backs of the two hands, and further contact between the electrodes and the skin was made with the kaolin paste. We had always thought that the paste was necessary in order to eliminate polarization. With this electrode no paste is used; the polished surface of the zinc is applied directly to the skin. Thus, it became possible to explore the skin without covering the body with kaolin paste. Furthermore, this electrode eliminates a drop in skin resistance produced in some instances by stimulation from the kaolin paste.

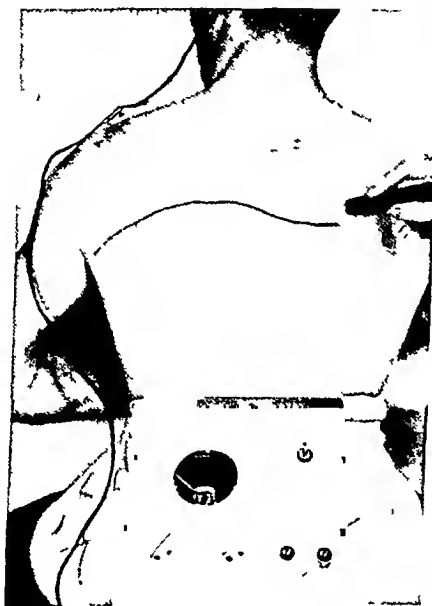


Fig 1

The electrodes were connected to a dermometer or an ammeter. The dermometer, described in detail by Levine,<sup>20</sup> had been used for most of our previous studies on skin resistance. It has two dials, one to show the amperage of the current flowing through the circuit, the other the resistance offered to the current.

A simple and less expensive instrument for this purpose was built for us by Mr. Frederick Whelan, of the Department of Electrical Engineering of the Johns Hopkins University. It contained an ammeter, a nine-volt battery, and a rheostat to adjust the voltage. Fig. 1 shows this instrument.

For the examination we used the following procedure. The patient was heated in a hot-air cabinet for a few minutes. After this the movable hand electrode was held gently against the skin on any part of the body and the voltage adjusted so that a small current flowed through the

circuit. Then the electrode was moved quickly from place to place over the surface of the body in jumps of approximately 6 inches. When a sudden change in the flow of the current was found, that is, either an increased or a decreased flow, the region was further explored until the line of demarcation between the areas of high and low resistance was located. This point was marked with a soft skin pencil (black for white patients and white for colored patients). Often the change from high to low resistance occurred within a few millimeters. When a second point of demarcation was determined, a line was drawn through the two points. The process was repeated at a distance of several inches at either end of the line until finally the entire areas of high and low resistance were defined.

An attempt was made to keep the current below the range in which it could be felt by the patients. The sudden fall in resistance from millions of ohms to only a few thousand ohms made it difficult always to make certain that the current remained imperceptible. The first tingling sensation reported by the patient usually came simultaneously with the drop in resistance.

The present report contains records made on 20 patients operated upon at Johns Hopkins Hospital and at the Baltimore City Hospital at Bayview and at two other hospitals in other cities. Five of the patients had upper thoracic and 15 had lumbar sympathectomies. Six patients had Raynaud's disease, 3 Buerger's disease, 3 arteriosclerosis, 3 hypertension, 2 chronic leg ulcer, 1 acrocyanosis, and 1 postphlebitic edema. The upper thoracic sympathectomy closely conformed to the operation used by Smithwick.<sup>21</sup> The white and gray rami from the second and third ganglia were sectioned, about 1 inch of the anterior and posterior roots of the second and third intercostal nerves removed, and the chain below the third ganglion sectioned. The third ganglion was brought out through the incision and sutured to a muscle in order to prevent regeneration. Since the ganglia which carry the sympathetic nerves to the arms remained in connection with the extremities, this represents a preganglionic type of sympathectomy. The lumbar sympathectomies also were usually of the preganglionic type, including the removal of the ganglia either at  $L_1$  and  $L_2$ , or at  $L_1$ ,  $L_2$ , and  $L_3$ , or at  $L_2$  and  $L_3$ . However, in some patients the operation was at least partially of the postganglionic type, including the removal of the ganglia at  $L_4$  or at  $L_4$  and  $L_5$ . In one patient operated upon in another hospital the removal must have included only the ganglia at  $L_4$  and  $L_5$ .

Records were taken at ordinary room temperature immediately after the patients had been heated for a few minutes in a hot-air cabinet.

The relation of the areas of high resistance to areas which do not sweat was determined by means of the Minor starch sweating test.<sup>22</sup> The skin was painted with a mixture of castor oil and iodine. After this mixture had been allowed to dry, an even layer of rice starch powder was dusted over the skin. Then the patient was heated in a hot-air

cabinet until active sweating started. The moisture from the sweat dissolves the starch and turns the mixture black. Areas which do not sweat remain white. The sweating test was made immediately after the completion of the skin resistance test and while the lines of demarcation were still on the skin. The two areas were superimposed upon one another, and thus we could compare them accurately.

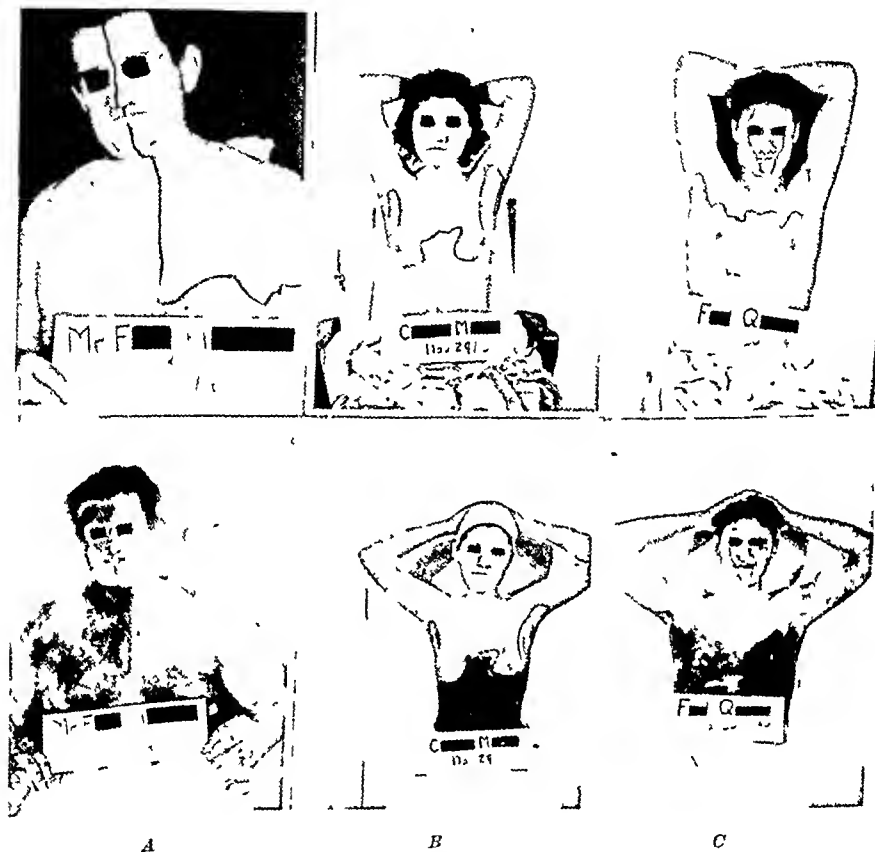


Fig 2

## RESULTS

The photographs in Fig 2 show the patterns obtained from three patients with dorsal sympathectomies. The first patient, a man 38 years of age (Fig 2A), had had a left dorsal sympathectomy for Raynaud's disease four months previously. The photograph at the top shows the area of high resistance, which included the left half of the face and neck and the chest just above the nipple, part of the axilla and the under surface of the arm, and a small area on the back about five inches below the level of the shoulders. The photograph at the bottom shows the results of the Minor sweating test. The black areas show active sweating; the white areas, no sweat. The high skin resistance areas and the areas which did not sweat show an almost exact cor-



responsiveness, except for an area on the right side of the mouth which did not sweat. This area often does not sweat in normal individuals.

Fig. 2B gives the photographs of a young woman with a bilateral dorsal sympathectomy. The area of high resistance included her head, neck, and chest below the breasts, the axillae, and a line across her back at the same level. The Minor test again showed a close correspondence between areas of sweat gland activity and high skin resistance, except for

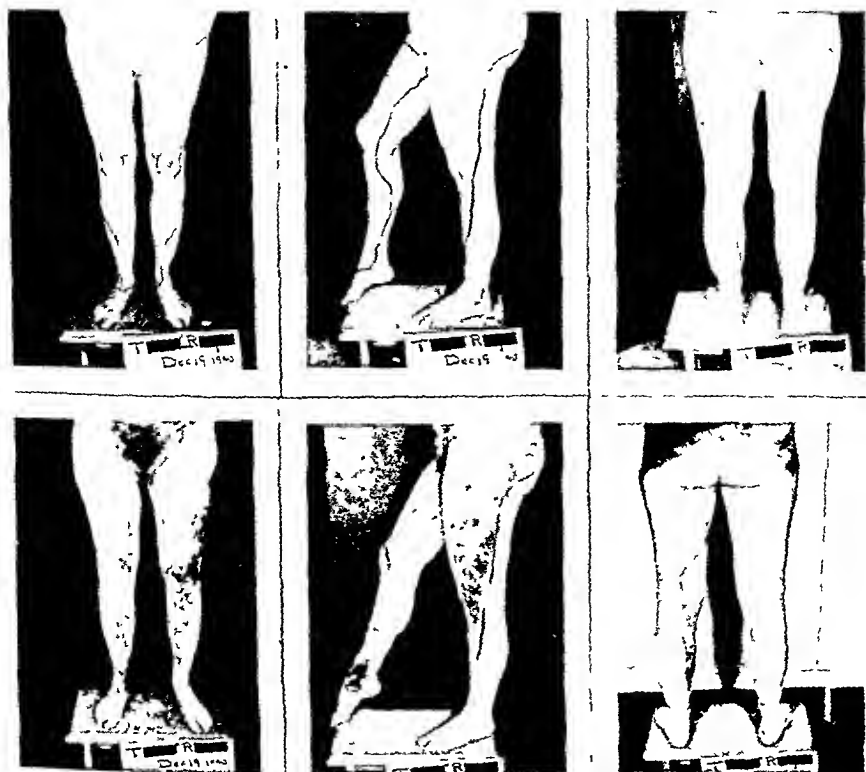


Fig 3

the skin on the breasts which showed many punctate areas of sweat up to a line at the anterior level of the breasts. At this line the skin resistance dropped to a lower level than in the mam large areas, but not down to the level of the resistance of the skin on the rest of the body. Such areas of partial decrease in skin resistance, which must indicate that some sympathetic innervation still remained and which we have found in other patients, we call "zone" areas. These areas must result from overlapping of the distribution of the adjacent dermatomes.

Fig. 2C gives the photographs of a man on whom a bilateral dorsal sympathectomy had been performed eight months before for Raynaud's disease. The area of high resistance was similar to those found in the other two patients, except for a small "zone" area on the face. In the

Minor sweating test this area contained several patches of black spots. It is possible that this area received some fibers from the first thoracic nerve.

These patterns of skin resistance and sweating closely agree with those which have been described by List and Peet<sup>23</sup> and others who used only the Minor test.

Lumbar sympathectomy produced high skin resistance areas with patterns which hitherto had not been described. Fig. 3 shows three views of the same patient with the skin resistance pattern and with the skin

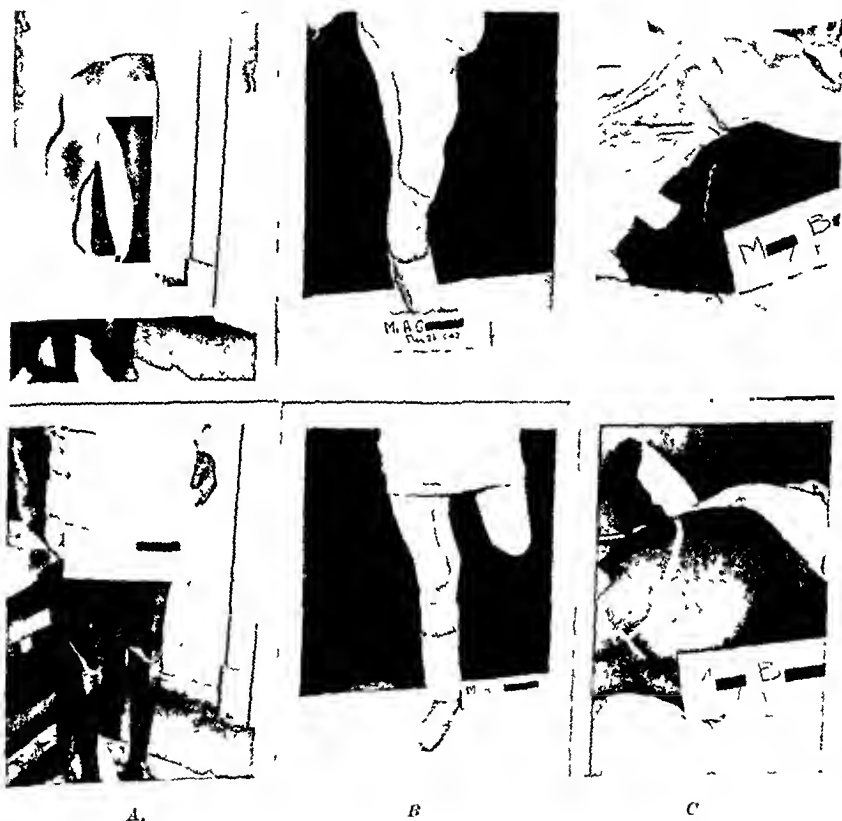


FIG. 4

resistance and sweating test patterns superimposed. The surgeon's notes stated that either  $L_2$ ,  $L_3$ , and  $L_4$  or  $L_3$ ,  $L_5$ , and  $L_6$  had been removed. The areas which again showed a close correspondence between skin resistance and sweating included the skin over the buttocks, down the posterior surface of the legs in a fairly narrow strip to the ankles, and over the backs and soles of the feet. In the 4 other patients who showed this pattern the surgeons stated that they had removed three ganglia below either  $L_2$  or  $L_3$ . A slightly different pattern is shown in Fig. 4A. The area of high resistance included the anterior as well as the posterior surfaces of the calves of the legs up to a line which fell

just below the kneecap. In the 5 other patients who showed this pattern the surgeons reported that 2 or 3 ganglia below  $L_1$  or  $L_2$  had been removed. Still another pattern is shown in Fig. 4B. In this case the area of high resistance included all of the posterior surface of the thigh and part of the anterior surface on the inside and above the knee. Two patients showed this pattern; in both the operation included the ganglia at  $L_2$ ,  $L_3$ , and  $L_4$ . The last pattern is shown in Fig. 4C. In this patient the area of high resistance included the entire surface of the leg in the front up to the groin and in the back up to the buttock. In this patient three ganglia below  $T_{12}$  had been removed. This is the only patient that showed this pattern.

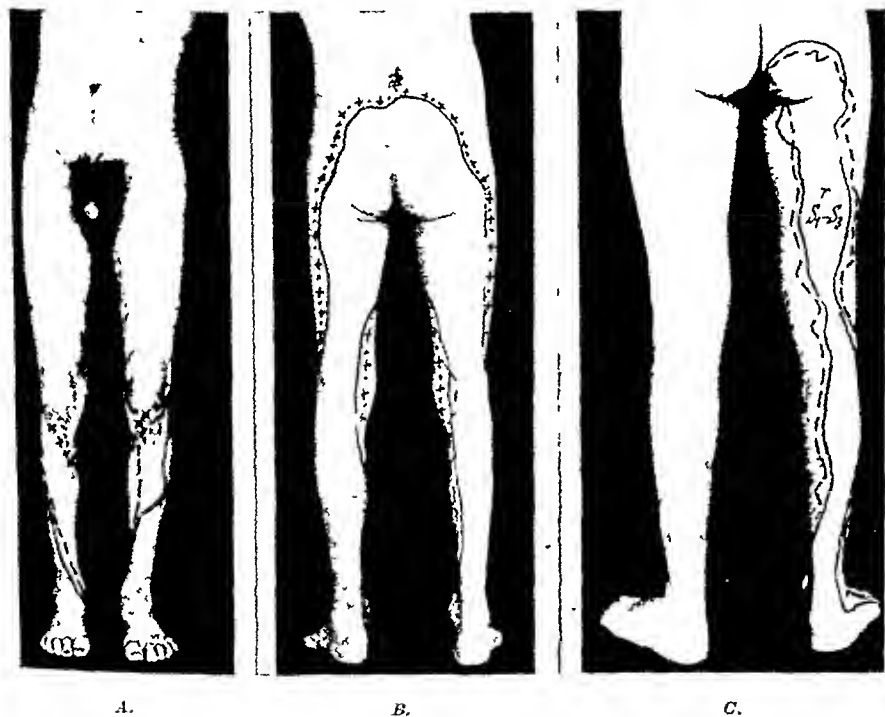


FIG. 5.

At the beginning of this study, when we had taken records on only a few patients, these different patterns did not seem to follow any special plan. We were most perplexed by the narrow area of high resistance which ran from the ankles up to the buttocks. The dermatome chart of the distribution of sensory nerves worked out by Head did not show any such well-defined areas, and Peet in his studies on sympathectomized patients with the Minor test had not found any pattern below the curved line across the upper border of the buttocks. Later, however, after we had taken records on more patients and had found with great consistency the same patterns, also after we had found that patients with lesions of sensory nerves below  $L_4$  showed anesthesia over a strip along

the posterior surface of the leg, we concluded that these areas of high resistance closely follow the distribution of the sensory nerves and that the pattern varied with the level of the gangliectomy. Figs. 5A and 5B show the areas of anesthesia mapped out by Foerster<sup>24</sup> on a patient with a traumatic transection of the cauda equina immediately below the outflow of the third lumbar nerve. It will be noted that these areas are almost identical with those shown in Fig. 3. Fig. 5C also taken from Foerster shows an even narrower strip area along the posterior surface of the leg in a patient with a resection of  $S_1$ ,  $S_2$ , and  $S_3$ . This area is almost identical with that on the left leg in Fig. 7B.

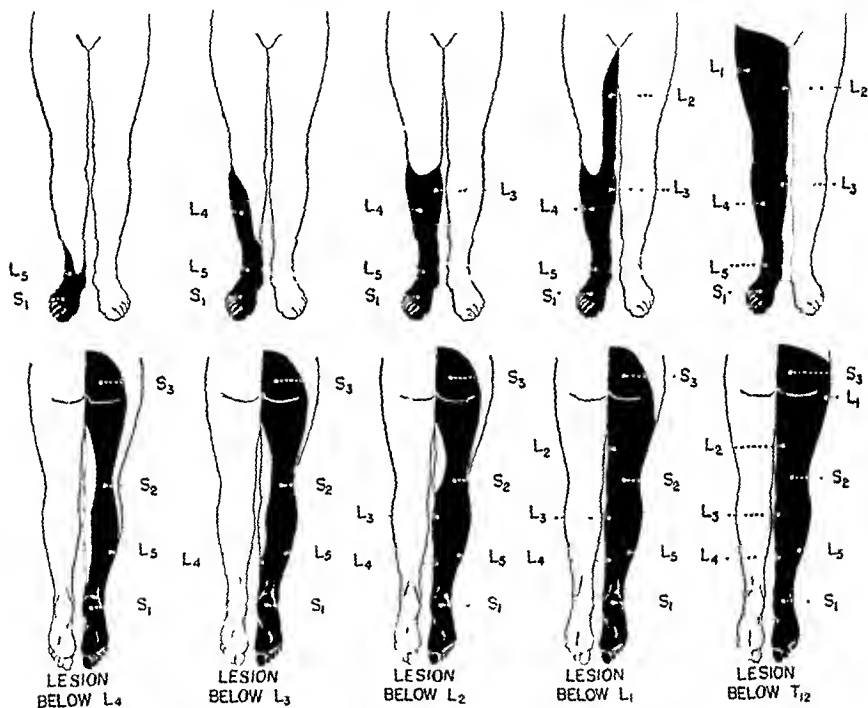


Fig. 6.

Fig. 6 gives a schematic representation of the different patterns arranged according to the level of the gangliectomy beginning with a section below  $L_4$  and ending with a section below  $T_{12}$ . The overlapping areas of the distribution of the sensory areas were taken from the distribution charts of Head<sup>25</sup> and of Foerster.<sup>24</sup> The latter was published by Fulton.<sup>26</sup> In these figures the arrows point not to the center of the sensory areas but to the lowest part of the area which overlaps with the adjacent dermatomes. When  $L_4$  was the last intact ganglion, the area of high resistance included  $L_4$ ,  $S_1$ ,  $S_2$ , and  $S_3$ . Each successively higher gangliectomy included more of the surface of the leg until finally it included the entire surface. Of the 15 patients, 1 showed the first pattern, 5 the second, 6 the third, 2 the fourth, and 1 the fifth; one with an unsuccessful operation showed no increased resistance at all. In nearly

every instance the location of the lesion worked out from the sensory distribution chart of the different patterns coincides with the level at which the operator stated that the lesion had been made, with the exception that in two patients in whom the surgeons stated that the first lumbar ganglion had been removed the area of high resistance did not include all of the anterior surface of the thigh. The discrepancies which existed may have been due to the variations in the location and fusion of the ganglia, as well as to the difficulties of identifying the different ganglia during the operation.

On the basis of this knowledge of the close correspondence between the sympathectomy and sensory dermatomes found for the various lumbar sympathectomies, it is possible now to state that the same principle applies also to the dorsal sympathectomies. According to the dermatome chart of Foerster, the overlap of the fourth dorsal dermatome should extend approximately  $1\frac{1}{2}$  to 2 inches above the level of the nipples. In the three patients described above in whom the lesion was made below the third lumbar ganglion, the lower border of the affected area was approximately 2 inches above the level of the nipples.

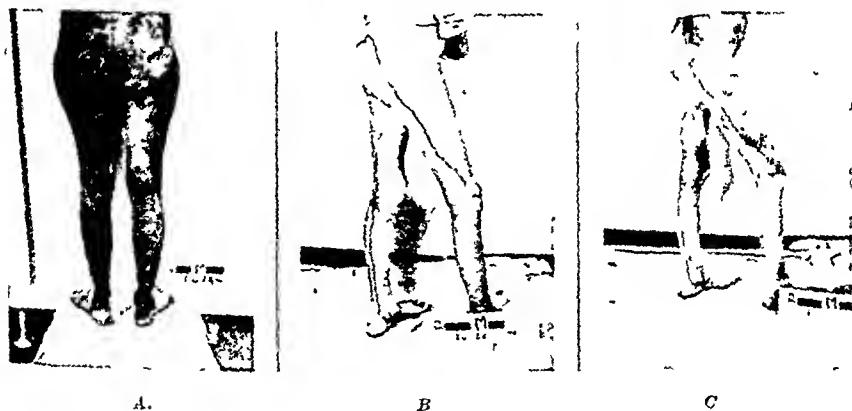


FIG 7.

Thus far we have used this method chiefly to determine within a few days postoperatively the results produced by sympathectomy performed at the Johns Hopkins Hospital and at the Baltimore City Hospital. We have also used the test to determine whether or not regeneration had taken place in patients operated upon two to three years previously and on patients operated upon in other hospitals in whom the success of the operation was doubtful. Fig. 7A shows the mapping of the high resistance areas in a patient who had had a bilateral lumbar sympathectomy two years before. On one side she showed the typical areas. On the other the skin showed the same level of resistance over its entire surface. The results of the Minor test confirmed this finding. This would indicate either that originally the chain on the left side had not been removed or that regeneration had taken place. Since the operation was successful on one side, it would seem likely that the removal had

been incomplete on the other side, thus allowing regeneration. Clinically symptoms of hypertension were again present in this patient.

We used the test for the examination of a patient brought to Johns Hopkins Hospital from another hospital. The patient suffered from Raynaud's disease. He stated that four months before he had had an abdominal nerve operation in another hospital for this condition. Clinically it was difficult to determine whether he had actually been sympathectomized. Our test showed no areas of high resistance on either leg. The Minor test showed an even distribution of sweating on both legs. It was concluded that the sympathetic chain must still be intact on both sides.

The same method was used in another patient who likewise had been sent here from another hospital. He showed severe Raynaud-like symptoms, which were, however, not entirely typical, in his feet, hands, nose, and ears. The report from the other hospital stated that a bilateral lumbar sympathectomy had been performed more than six months before. Clinically it was not clear that the sympathectomy had been performed. Some of the clinicians who saw the patient stated that he sweated; others, that he did not. A dorsal sympathectomy for his nose and ears was considered. However, the clinicians did not want to recommend this operation if a lumbar sympathectomy had been performed without any visible improvement. Skin resistance tests showed that lumbar sympathectomy had been performed on both legs, probably below  $L_2$  on one leg and below  $L_3$  on the other leg. The photographs in Figs. 7B and 7C show the areas. The Minor test completely confirmed our findings.

We have also had occasion to use this method for the examination of areas affected by ganglionic alcohol block. Here also, it gives a very sharp demarcation of the affected areas. Similarly, in three cases of spinal cord lesion we have also obtained sharply defined areas which corresponded to the location of the lesion in the cord.

#### DISCUSSION

Up to the present the Minor starch sweating test was the only available method for the determination of areas of skin on the head and on the body which had been affected by sympathectomy. This method has several shortcomings. It requires a considerable amount of time and skill to paint evenly the entire body, or only half the body, with the castor oil and iodine mixture and to cover it with the starch powder. Furthermore, after the test a shower and scrubbing are required to remove the mixture. On colored patients the results often cannot be interpreted; further, since many individuals do not sweat even when placed in the hot-air bath, its use is limited. The lines of demarcation between areas that sweat and those that do not are not always sharply defined. The failure of Peet to discover the pattern on the legs which we have found with the skin resistance method shows the shortcomings

of the starch method. However, once the presence of these areas was definitely known, special care in giving the Minor test also brought out the same pattern of sweating.

In contrast, the skin resistance method requires very little time. The mapping for cervical and lumbar sympathectomies requires only five to ten minutes. The lines of demarcation are sharp and remain quite constant from day to day. Only a small amount of external heat is necessary to bring out the difference in resistance in the different areas. The test can be made equally well on colored and white individuals and on individuals who do not sweat enough for application of the Minor test.

The results seem to establish a close correspondence between sensory and sympathetic dermatomes. The exact determination of the sympathetic dermatomes will have to wait for experimentation on monkeys or apes in which skin resistance mappings are made after removal of two or three ganglia. It is very likely that by means of the skin resistance method it will be possible to map out areas affected by removal of only one ganglion. The affected area would be expected to show itself as a "zone" area despite the overlapping of the two adjacent dermatomes.

These skin resistance tests show that the dorsal sympathectomy as performed by Telford,<sup>27</sup> Livingston,<sup>28</sup> and Smithwick<sup>29</sup> affects the head, neck, and all of the arm, except small areas under the armpit. It is fully adequate for sympathetic denervation of the upper extremities. The tests show that the removal of the second and third lumbar ganglia denervates all of the leg below the knee and all except the anterior surface of the thigh above the knee. This is in agreement with the conclusions arrived at by Smithwick<sup>21</sup> on the basis of clinical studies. Removal of the first lumbar ganglion, which denervates the entire leg, would probably be better, except for the fact that in men it interferes with ejaculation.

Since such a close correspondence exists between the areas of high resistance and the distribution of the sensory nerves, this test may be used in the mapping of areas of sensory loss; and it would have the additional advantage that it does not depend on cooperation on the part of the patient.

#### SUMMARY

1. A method was described by means of which areas affected by sympathectomy can be mapped on all parts of the body. These areas offer a high resistance to the passage of a very small direct current. The unaffected areas have the normally low resistance. The line of demarcation between the two areas usually is so sharp that the resistance may drop from many thousand ohms to only a few hundred ohms in less than  $\frac{1}{4}$  inch.

2. The areas of high resistance do not sweat. This was demonstrated by the Minor starch sweating test. The areas of high resistance and of nonsweat gland activity showed an almost perfect correspondence.

3. Twenty patients were studied with this method, 3 with dorsal sympathectomy and 17 with lumbar sympathectomy.

4. The areas of high resistance produced by sympathectomy closely followed the sensory dermatomes. The lumbar sympathectomy brought out this relationship most clearly. Five different patterns produced by lesions below T<sub>12</sub>, L<sub>1</sub>, L<sub>2</sub>, L<sub>3</sub>, and L<sub>4</sub> were demonstrated.

5. The method was applied in determining the success of sympathectomy, the areas of skin affected by the operation, and the presence of regeneration.

6. Similarly, skin resistance tests were used in localizing spinal cord lesions.

7. Compared to the Minor starch sweating test, the determination of skin resistance is simple and involves less time and discomfort for the patient; it can be used on colored as well as on white patients and on individuals who do not sweat sufficiently to color the starch paste; and it gives very sharp boundary lines between affected and unaffected areas.

8. Since this technique requires little or no cooperation from the patient, it should be useful for the mapping of sensory dermatomes.

We want to thank Dr. H. B. Shumacker, Jr., and Dr. I. R. Trimble of the Department of Surgery and Dr. F. R. Ford of the Department of Neurology for their very helpful cooperation.

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# NEPHROLITHIASIS DUE TO INFECTION WITH THE BACILLUS PROTEUS\*

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## BACILLUS PROTEUS

THE *Bacillus proteus* was first systematically investigated by Hauser in 1885. It is widely distributed in nature, having been found in soil, decomposing animal matter, and in human and animal feces. It is a pleomorphic, motile, gram-negative rod one to thirty microns in length, and rapidly forms a spreading "ground-glass" layer on solid media, in which it liquefies gelatin and produces indol, phenol, nitrites, hydrogen sulfide, and ammonia (Meyerhof). It is finally identified by its fermentation of certain sugars to acid and gas (Topley and Wilson). Inoculated into animals, it may die, produce abscesses, or cause septicemia. It is only weakly antigenic. In man it has caused infections in the middle ear, mastoid, meninges, intracranial sinuses, eye, nose, throat, gall bladder, peritoneum, female internal genitals, bones, testes, and urinary tract.

## INFECTION OF URINARY TRACT

According to Cabot and Smith the *B. proteus* probably reaches the urinary tract only through instrumentation, although Chute has had 2 cases in which there was no such history.

Schulte did not find it in an investigation of the bacterial flora of the urinary tract, Streng having found it in such circumstances in but 3 of 33 cases. Important factors in localization are stasis, recumbency, and wasting diseases.

It is a common resident of the human bowel, Dr. M. Levine, bacteriologist at the University of Minnesota Hospitals, having found it on a single culture of the stool in 22 of 53 consecutive patients taken at random from the wards as well as in 4 of 6 bed sheets used by patients without clinical evidence of infection with *B. proteus*. Thus, it is clear that the organism may be present about the external urinary meatus and may be introduced by an urethral instrument, or may grow along the outer surface of an inlying catheter. Such a catheter, whether in the urethra, a suprapubic fistula, or in the kidney, may be contaminated either directly or from linen not grossly soiled.

The route by which the organism, having been introduced into the bladder, invades the kidneys, is not definitely known, but Scott found *B. proteus* in the blood in 5 of 82 patients with urethral chill, suggesting arrival by way of the blood stream. Theoretically, of course, it may

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ascend the periureteral lymphatics or the lumen of the previously diseased ureter or follow the lymphatics from the ascending colon to the right kidney. The latter route may account for infections in the absence of instrumentation.

According to the literature, *B. proteus* is not a very common invader of the urinary tract, having occurred in 135 (5.4 per cent) of 2,502 cases of urinary infection in five reported series (Cabot, Streng, Kretschmer and Mason, Scott, and Scott and Sandholzer).

#### MECHANISM OF FORMATION OF STONE

The relative infrequency of infection with *B. proteus* is in striking contrast to its potential seriousness to the afflicted individual. Its peculiar menace is due to its ability to break down the urea of the urine into carbon dioxide and ammonia, the latter of which makes the urine strongly alkaline. The urea is apparently attacked by an enzyme contained in the bacterial cell, since killed and desiccated cultures can split urea, although it is impossible to extract an urease from the living organism (Day and co-workers).

The clinical importance of this alkalization of the urine was recognized as early as 1901 by Brown, of Baltimore, who reported 5 cases of stone due to infection with urea splitters, for 3 of which *B. proteus* was responsible. Stone formation in such cases is due to the precipitation of the phosphates and carbonates of calcium, magnesium, and ammonia in the alkaline urine. The precipitate may gather about a bit of necrotic tissue (Keyser), fibrin (Lazarus), or a clump of bacteria (Rovsing); or it may become adherent to an ulcer and later drop off (Hager and Magath).

*B. proteus* is not the only organism which can split urea. Hellström has written extensively about this phase of staphylococcal infection of the kidney; according to Chute, certain strains of streptococci, *B. pyocyaneus*, *Haemophilus influenzae*, diphtheroids, micrococci, and many strains of *E. coli* also have this faculty. Higgins has stated that 9 per cent of bacilli found in conjunction with nephrolithiasis can decompose urea.

Other known factors in the development of nephrolithiasis in general are summarized in Table I. In all probability the urea splitters can form stones in the absence of all of the systemic and perhaps in the absence of the local factors, although the presence of any or all of the latter increases enormously the danger of stone formation once such organisms gain access to the urinary tract.

#### INCIDENCE OF INFECTION BY *B. PROTEUS* IN NEPHROLITHIASIS

*B. proteus* is found in but a small proportion of renal and ureteral lithiasis. Of 2,537 examples of stone collected from ten reports in the literature (Rovsing, Priestley and Osterberg, Eisenstadt, Lett, Chute, Dege, Smith, Korhonen, Harrington, Chute and Suby), data as to infec-

TABLE I

## KNOWN FACTORS IN THE PRODUCTION OF NEPHROLITHIASIS

## I. Systemic

- A. Deficiency of vitamin A
- B. Persistent ingestion of alkali
- C. Overconcentration of the urine
- D. Increased excretion of calcium
  - 1. Hyperparathyroidism
  - 2. Diseases of bone
    - a. Osteomyelitis
    - b. Atrophy (immobilization)
  - 3. Ingestion of acids (?)
- E. Increased excretion of uric acid (gout)
- F. Cystinuria and xanthinuria

## II. Local

- A. Stasis of urine
  - 1. Obstructive lesions
  - 2. Recumbency (stagnation in dependent calices)
- B. Submucosal necrosis of renal papilla
- C. Trauma
- D. Foreign body
- E. Infection with organisms splitting urea

tion were complete in 2,191. Sixty-five per cent of these were associated with bacteria in the urine. In 6.2 per cent of the whole group and in 11 per cent of those infected, *B. proteus* was found.

The organism occurs relatively more often in the presence of recurrent stones than in primary stones. Swift-Joly and many others find that nearly all recurrent stones are associated with infection and that if post-operative infection with urea splitters occurs, recurrence is almost certain to take place. Chute reported that 13 of 26 recurrent stones were due to infection with *B. proteus*, and Twinem found the organism in 7 of 10 patients with repeated recurrences after operation.

COURSE OF LITHIASIS FROM *PROTEUS*

Once stones begin to form in the kidneys as a consequence of infection with *B. proteus*, the outlook is black indeed unless stones, predisposing causes (particularly stasis and immobilization in recumbence), and the exciting organism can all be removed. If the urinary tract is normal except for the infection, the *B. proteus* is easily killed by acidification of the urine and the administration of mandelic acid; but if hydro-nephrosis is present, or if the patient is necessarily immobilized in recumbency as in extensive paralysis or multiple severe fractures the outlook is very grave. In neither instance is it ordinarily possible to acidify the urine; in the latter situation the stasis in dependent calices and the increased excretion of calcium resulting from atrophy of bone may render treatment futile.

## TREATMENT

If treatment is to be successful, the presence of *B. proteus* must be discovered and its serious significance appreciated. This can be done

only by proper culture, since it cannot be differentiated from other gram-negative rods in stained smears. It is imperative, therefore, that the urine be cultured in every case of infection and of stone, and that it be cultured at short intervals following any type of operation upon the kidney which involves postoperative drainage of urine to the outside.

After an operation for stone before which the urine was sterile, the greatest pains must be taken to prevent infection with any organism. Since *B. proteus* is a common inhabitant of the bowel, the dressing should be covered with sterile waterproof sheeting to prevent contamination from the bedclothes if the dressing becomes soaked.

If a pelviostomy or nephrostomy is used, special care must be taken in the preparation and handling of the tubing before, during, and after operation. Chute has called attention to the tendency of *B. proteus* to survive attempts at sterilization of rubber tubing containing deposits of urinary salts. This tendency can be circumvented only by constant vigilance. A catheter which has been used for continuous drainage of urine must be soaked in hot soapsuds, then in dilute acetic acid, and then cleaned by drawing gauze through its lumen and rinsing it extensively. If any deposit of salts remains, the catheter should be cut up and discarded. If perfectly clean, it should be autoclaved. Glass connectors and receiving bottles must be cleansed with a mineral acid, rinsed, and autoclaved. The rubber tubing used to connect the catheter to the receiving bottle cannot be sterilized adequately after use because of its length. New, cheap tubing carefully rinsed and autoclaved should be used for each patient and discarded.

It is equally important that the drainage system be kept closed to avoid contamination from the air. A simple method of doing this is to use a two-hole rubber stopper. One hole contains a long glass tube which is connected to the drainage tube. The other holds a short glass tube capped with sterile gauze. The whole assembly is sterile, and the collecting bottle is changed daily (Fig. 1).

Reserve supplies of these kinds should be cultured periodically to make certain that a proper procedure is being followed and is effective.

Immediately after the operation, fluids should be forced to insure diuresis, the patient turned frequently to avoid stasis in dependent calices, and one of the sulfonamides used in small doses from the day of operation as an aid in preventing infection, as advocated by Stalker and Schulte.

The stone should be analyzed at once. If it consists of phosphates and carbonates, it is desirable, as soon as the postoperative reaction has subsided, to acidify the urine to a pH of 5.4 or below and thereafter to give mandelic acid and to limit fluids until any infection has been overcome. Because most preparations of mandelic acid contain ammonia or calcium and because acidification of the urine may increase the excretion of calcium (Albright, Sulkowitch, and Chute), this regime probably should not be continued after sterilization of the urine. If it proves impossible

to acidify the urine, and thereby to sterilize it, or if the stone is of a type formed in acid urine (oxalates, urates), the sulfonamides should be continued until the urine is sterile.

Upon subsidence of the postoperative reaction, the patient should receive an adequate mixed diet with an abundance of vitamins.

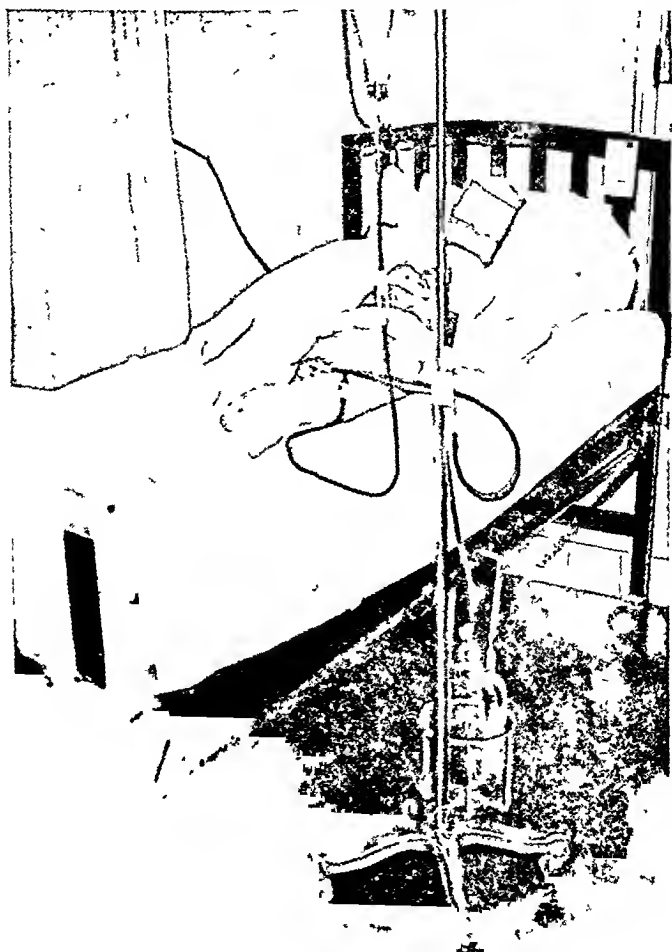


Fig. 1.—Apparatus for continuous drainage of urine and continuous irrigation of bladder with 0.8 per cent sulfanilamide

If the *B. proteus* or another urea splitter is found *before* operation, and if the stones appear soft and crumbly or are multiple, operation probably ought to be deferred until the stones become denser and more discrete, or consolidate, or both, because of the certainty of recurrence around any sand left behind. At operation great care should be taken to remove all fragments; success should be verified by x-rays made on the operating table.

Nephrostomy is imperative to avoid postoperative obstruction, to afford escape for blood and other detritus which might form the nu-

cleus of a new stone, and to permit acid irrigations. The last are intended both to afford an unfavorable culture medium for the urea splitters and to dissolve any sandy material left behind, although the latter is more to be hoped for than expected. The preferred solution is the mixture of citric acid and sodium citrate evolved by Albright, Sulkowitch, and Chute (sodium citrate, 45.2 Gm.; citric acid, 38 Gm.; and distilled water, 1 liter). This may cause considerable irritation and have to be diluted, discontinued, or alternated with saline solution. In suitable cases it may even be used as a drip.

During convalescence sulfathiazole should be given in full doses, substituting sulfanilamide or sulfapyridine if the first is ineffective in killing the organisms.

The nephrostomy should be maintained until the urine is sterile or until stasis is overcome so that the urine can be acidified to a pH of 5.4 and kept there, when mandelate may be started and the tube withdrawn. It is impossible to overemphasize the importance of aseptic handling of the nephrostomy tube and of everything connected with it; it is difficult to convince interns and nurses that a fleeting contact between the open end of the tube and the bedclothes during irrigation or the use of a syringe or solution of doubtful sterility may defeat the whole purpose of the surgical removal of a stone; yet it is so.

By these methods recurrences can be minimized, although Chute found that 74 per cent of patients operated upon for stone in the presence of urea splitters had recurrences within three years. Swift-Joly states that: "If the infection is caused by a urea splitting organism, it is most probable that a secondary phosphatic calculus will form in a short time." He has observed recurrence in 16 per cent of aseptic and 50 per cent of infected renal calculi.

Because of the frequency with which instrumentation precedes infection with *B. proteus*, most such infections can be prevented by proper attention to the details of asepsis in the use of urethral instruments and especially of indwelling catheters and cystostomy tubes. In addition, the same regime recommended after lithotomy should be observed during drainage of the bladder; i.e., the use of sulfonamides or of acidification and mandelic acid, an adequate diet and fluid intake and, above all, aseptic handling of sterile tubing and bottles.

#### CASE REPORTS

Our own material at the University Hospital is too small to permit any statistical computations. In the period from July, 1930, to January, 1940, renal and ureteral calculi were diagnosed 495 times. *B. proteus* was found in the urine on culture in 12 cases (2.4 per cent). Nine of the 12 were admitted during the last four years. This is due in part to the operation of chance, in part to the increasing frequency of urethral instrumentation, and in part to more careful and more frequent bacteriologic studies of the urine, based upon realization of the

serious significance of infections with this organism after painful experiences with the first 3 cases. The cases have been divided, rather artificially, into those following: (1) operations upon the bladder, (2) operations upon the kidney, (3) use of inlying catheter in patients profoundly ill, and (4) apparently spontaneous infections.

#### CASES FOLLOWING OPERATION UPON THE BLADDER

H. N. (No. 608824), aged 22 years, had a cystostomy in September, 1932, by another physician because of a contracted bladder of unknown etiology with bilateral hydronephrosis and hydroureter. Six weeks later he was admitted with the tube clogged; he had multiple calculi in the left kidney and *B. proteus* in the urine. By January, 1933, he had bilateral calculi which were growing rapidly; left pelviolithotomy and nephrostomy in March, 1933, were followed by prompt recurrence. Despite acid irrigations, the use of neoarsphenamine and ketogenic diet, and the passage of many stones from both sides, the patient slowly failed and died on July 28, 1934. Necropsy disclosed interstitial cystitis, bilateral hydronephrosis, pyelonephritis with abscesses, and nephrolithiasis.

*Comment.*—This was my first experience with what might be called "malignant" nephrolithiasis due to implantation of *B. proteus* into hydronephrotic kidneys. The lessons learned then have been slowly sinking in ever since.

S. B. (No. 616637), aged 31 years, admitted in September, 1934, had an encrusted cystitis with *E. coli*, staphylococci, and diphtheroids. It had resisted every form of conservative treatment for five years, wherefore presacral neurectomy and curettage of the bladder were done after admission. There was temporary benefit, but six weeks later she returned with hydronephrosis and acute bilateral pyelonephritis due to *B. proteus*. Bilateral pelviolithotomy and permanent nephrostomy were finally necessary.

She died under unknown circumstances outside the hospital three years later.

*Comment.*—*B. proteus* apparently followed the cystostomy tube to the bladder and then regurgitated to the kidneys. Stones formed and grew rapidly; their removal and nephrostomy were inadequate to control the process despite energetic irrigations and the use of all available antiseptics.

L. H. (No. 634521), aged 21 years, admitted in January, 1935, from another hospital, had been in an automobile accident six months before. He had a fractured pelvis, suprapubic, perineal, and rectourethral fistulas, and multiple calculi in the right kidney and bladder, infection with *B. proteus*, and malnutrition.

Despite a series of efforts, including urinary antiseptics, litholapaxy, colostomy, irrigations, and dietary management, he died in August, 1936, of chronic pyelonephritis, nephrolithiasis, uremia, and amyloidosis.

*Comment.*—The initial injury was very severe; the complications more so; every measure tried proved ineffective. All 3 of these cases emphasize, by default, the value of the sulfonamides.

D. M. (No. 686663), aged 7 years, admitted Oct. 30, 1939, had a large ureterocele with 300 c.c. of residual urine infected with streptococci and *Staphylococcus albus*. There was bilateral duplication of pelvis and ureters with one functionless segment on each side and regurgitation up the ureters.

The ureterocele was excised and cystostomy made on Nov. 7, 1939, and he was sent home with drainage aimed at improving renal function. In February, 1940, he had *B. proteus* in the urine, a calculus in the functioning segment on the right, three in its ureter, and two in the functioning segment on the left (Fig. 2). In March, 1940, right pelviolithotomy, nephrostomy, and heminephrectomy were done, and *B. proteus* was eradicated later with sulfathiazole. A drip of citric acid-sodium citrate was then attached to the nephrostomy; in three weeks the ureteral calculi were gone.



Fig. 2.—Case D. M. Calculi following infection with *B. proteus* through a cystostomy.

In August, 1940, the left renal calculi passed into the ureter; left heminephrectomy and nephrostomy were done. In October, 1940, the citrate drip was started on the left; in eleven days the stones and *B. proteus* were gone (Fig. 3). The nephrostomies are being maintained pending recovery of the bladder.

*Comment.*—This is a striking demonstration of the value of sulfathiazole and the citric acid-sodium citrate combination; it is a question whether the child has enough renal function to permit growth and whether the terrifically damaged bladder will ever become useful.

K. D. (No. 694539), aged 36 years, admitted on April 23, 1940, had a recurrent giant left renal calculus with pyuria and *B. proteus*. A bladder tumor had been



fulgurated elsewhere in 1931; a branched left renal calculus had been removed by another surgeon in 1934, at which time cultures showed *E. coli* and streptococci; a fistula had been present intermittently since.

Left nephrectomy on April 27, 1940, was followed by recovery. Both sulfanilamide and sulfathiazole were used postoperatively. On Nov. 14, 1940, the urine and KUB were negative and the patient symptom free.

*Comment.*—Unilateral calculous pyonephrosis due to *B. proteus* presents no special problem other than eradication of the organism from the bladder postoperatively.



Fig. 3—Case D. M. Calculi dissolved by continuous irrigation with citric acid and sodium citrate through nephrostomies.

#### CASES FOLLOWING OPERATION UPON THE KIDNEYS

V. T. (No. 636931), aged 25 years, was admitted on March 28, 1935. Six years before he had received intensive local treatment elsewhere for gonorrhea. For two years he had had a mild lumbar backache. The general state was excellent. The urine contained pus and staphylococci; KUB showed a branched stone on the right, two bean-sized calculi in the left pelvis, and one in the left lower ureter.

On April 12, 1935, left pelvolithotomy and pelviostomy, and on April 30, left ureterolithotomy were performed. Irrigations with 1 per cent silver nitrate were

carried out. On May 16, 1935, the urine from both kidneys contained *B. proteus*. Nevertheless, right nephrolithotomy and nephrostomy were done in September, 1935. Both pelvises were then lavaged weekly with silver nitrate on eleven occasions. The ketogenic diet and neoarsphenamine were without effect. In January, 1936, culture showed *B. proteus* on both sides, after which he abandoned treatment.

On Dec. 3, 1940, he was well but had an occasional white cell and *E. coli* in the urine. The KUB was negative.

*Comment.*—This patient was evidently infected by staphylococci during treatment for gonorrhea and developed four stones. *B. proteus* was introduced into both sides by drainage tubes after lithotomy. Nevertheless, because he was robust, he had no systemic disease, no stasis, and resumed normal activity, *B. proteus* disappeared spontaneously. That he is well five and one-half years later is due at least as much to good luck as to good management. He is now under treatment to eradicate *E. coli*.

B. H. (No. 671576), aged 28 years, admitted Nov. 21, 1938, had left renal colic of two months' duration. There was a stricture of the left ureteropelvic junction with a small hydronephrosis and a minute shadow in the right renal area. The urine was sterile. Dilatation of the left ureter being ineffective, a Y-plasty was done on Nov. 22, 1938. In a culture made on the day of operation, *B. proteus* was found in urine from the bladder; its significance was not appreciated.

Fifteen days after operation there was a right renal colic. A small calculus was pushed from the upper ureter into the pelvis, urine from which contained *B. proteus*. Thereafter acidification of the urine was impossible and sulfanilamide ineffective. Stones were passed intermittently from the right until readmission on Aug. 23, 1939, with fever and right renal pain. At operation fibrin and sandy material were removed from the inflamed right kidney, and nephrostomy was done. Bleeding occurred into the wound that night, and the patient died despite transfusion, evacuation of clots, and packing.

At necropsy, the hemorrhage was found to have come from an ureteral vessel. The left kidney was normal except for a little scarring.

*Comment.*—*B. proteus* was introduced at cystoscopy and overlooked. There is evidence that a silent calculus was present on the right before operation, but it was the introduction of the organism that led indirectly to death which could have been prevented by the nephrectomy which seemed at the time unwise.

H. J. (No. 654859), aged 38 years, was admitted Nov. 9, 1937, for disabling bilateral backache of long standing, not relieved by ureteral dilatation, and due to low-grade bilateral obstruction at the ureteropelvic junction, with sterile urine. In November, 1937, a right Y-plasty was done. Recovery was uneventful, but a month later urine drained from the wound until a small stone was passed. *B. proteus* was then found in the urine but responded to sulfanilamide.

Left Y-plasty was done in June, 1938. Recovery was uneventful, but he returned in two months with a left renal colic, a stone 2 cm. in diameter in the left kidney, and pyuria with *B. proteus*. On August 9 left pelvolithotomy was performed and the urine sterilized by 6 Gm. of sulfanilamide daily for three weeks.

In June, 1940, excretory urography showed no calculi, and in August the urine was sterile.

*Comment.*—One wonders at the temerity of both patient and surgeon in wanting a second operation after the experience with the first, yet sulfanilamide unquestionably saved the day.

M. B. (No. 675383), aged 58 years, was admitted Feb. 6, 1939. For two years he had had left renal colics and pyuria, due to bilateral multiple calculi with pus and diphtheroids in the urine. After left pelvioneephrolithotomy and nephrostomy in February, 1940, *B. proteus* was somehow introduced, and although recovery was good, recurrence was prompt. Because of the presence of hydronephrosis and calculi, it has been impossible to destroy the organism. Curiously enough the patient has remained symptom-free, although his outlook is not good.

*Comment.*—Operation defeated by the introduction of *B. proteus*.

#### CASES DUE TO THE INLYING CATHETER

E. J. (No. 686081), aged 27 years, was placed in the respirator because of bulbar poliomyelitis with retention of urine in September, 1939. The urine on admission contained pus, *E. coli*, gamma streptococci, and *Staphylococcus albus*.

Despite many attempts at acidification, the use of sulfanilamide, and sufficient recovery to permit sitting up and removal of the catheter, *B. proteus* appeared first on Feb. 18, 1940, resisted treatment, and caused death on April 14, 1940. Necropsy disclosed acute bilateral pyelonephritis with multiple abscesses and calculi.

*Comment.*—Better care of the inlying catheter would have prevented this all too common outcome in a patient with temporary paralysis of the bladder. Such occurrences, so frequent after injuries to the spinal cord, are a reflection upon the handling of patients with paralyzed bladders.

J. S. (No. 685656), aged 47 years, was confined for several months in another hospital because of fractured ribs, spine, and skull. He was at first unconscious and had an inlying catheter. In August, 1939, two months after discharge, left renal colics led to admission to the University Hospital. In September he had a branched calculus on the right and a stone 2 cm. in diameter on the left (Fig. 4). Left pelviolithotomy, nephrostomy, acid irrigations, and sulfathiazole killed the *B. proteus* on the left. In January, 1940, the same procedure was followed on the right, and he was discharged, free from *B. proteus*, on Feb. 24.

In June, 1940, he was symptom-free, x-ray was negative, and the clear urine contained a "coagulase negative" (presumably nonpathogenic) staphylococcus.

*Comment.*—The apparently successful issue depended upon disappearance of the predisposing causes (immobilization, bone atrophy, inlying catheter) and careful postoperative eradication of the organism.

F. H. (No. 691126), aged 39 years, was admitted in shock due to right renal colic and fever in March, 1940. She proved to have a bilateral duplication of the renal pelvis and ureter with calculi in the right upper segment and its ureter, and in the left lower segment, both infected with *B. proteus*. Her condition was precarious. The blocked right upper segment was drained with an inlying catheter, and the ureteral stone was finally pushed into the pelvis. Right pelviolithotomy and nephrostomy were done on April 20, 1940. The *B. proteus* was killed by irrigations and sulfathiazole.

On July 15, 1940, left heminephrectomy was done, because the stone was crumbly and adherent. *B. proteus* was absent from the urine on both sides at discharge, but on Nov. 30, 1940, she had three small calculi in the right lower (unoperated) pelvis, and the urine contained *E. coli*; she was pregnant.

*Comment.*—The calculi in the lower segment probably formed before the *B. proteus* was eradicated. The persistence of *E. coli* and the past history make therapeutic abortion and sterilization imperative.



FIG 4.—Case J. S. Calculi due to infection by *B. proteus* through an indwelling catheter

#### APPARENTLY SPONTANEOUS

Mrs. F. L. (No. 699880), aged 63 years, was admitted on Oct. 10, 1910, because of severe pain in the left flank of two months' duration. There was no history of instrumentation. She was obese and quite feeble and proved to have a left calculeous pyonephrosis with purulent urine containing *B. proteus*. Because of her poor general state, nephrostomy was done on Oct. 15, 1910, and her general condition improved. Nephrectomy was done on Dec. 18, and recovery was satisfactory.

*Comment.*—Unilateral destructive disease with a sound opposite kidney presents no special problems and has but one solution.

## SUMMARY

Thirteen cases of nephrolithiasis secondary to infection by *B. proteus* have been reported. The organism, resident in the bowel, is usually introduced into the urinary tract by or through the catheter, forms ammonia from the urea of the urine, thus alkalinizing the urine and precipitating the phosphates and carbonates of calcium, ammonia, and magnesium, especially in the presence of stasis, recumbency, and increased excretion of calcium.

In 11 of the 13 patients (84 per cent) it is known to have been introduced by catheters, usually employed as nephrostomies or cystostomies. In 2, congenital anomalies of the urinary tract were present. In 9 (70 per cent), the calculi were bilateral; 2 grew very rapidly under observation. Five (38 per cent) of the patients died, 4 as a direct result of the infection and lithiasis, and 1 from a surgical accident.

Treatment was entirely futile in the earlier cases but is gradually improving for four reasons: the development of effective urinary antiseptics (sulfanilamide and especially sulfathiazole) and the citrate-citric acid irrigant; a clear understanding of the mode of entrance of the organism into the urinary tract; an appreciation of its extraordinarily serious potentialities; and comprehension of the role of predisposing factors such as stasis and recumbency.

As a result, 7 patients have been apparently cured of the infection, and 6 of the stone-forming tendency by a combination of operation and sulfonamides, and in suitable cases, irrigations with citrate-citric acid.

Three must be classified as cures more or less by default, since 2 followed nephrectomy for unilateral disease, and 1 occurred spontaneously after removal of calculi. Two of the "cured" patients have *E. coli* but not pus in the urine, and 1 has calculi in the unoperated segment of a double kidney, apparently having started these stones before the organism was eradicated.

The real solution of the problem lies, however, not in removing stones, relieving stasis, and curing infection, but in preventing the entrance of the organism into the urinary tract by adequate, painstaking, and persistent attention to the proper sterilization of catheters and their adjuncts, to their aseptic introduction and fixation, and above all, to the proper care of systems draining urine from the body. To this end, educational activities by informed urologists are imperative.

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## EXTRADURAL HEMORRHAGE IN THE POSTERIOR FOSSA

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**D**ISCUSSION of extradural hemorrhage in the literature has been restricted almost exclusively to those clots which result from laceration of the trunk of one of the branches of the middle meningeal artery. Clots from this source cause rapid and direct cerebral compression. In typical cases they are readily recognized, but inasmuch as they do not always develop classical symptoms, the mortality continues high because of late diagnosis.

Extradural hemorrhage from a lacerated sinus of the cerebral dura is rare, but some recognition is given in the literature to the possibility of clots from this source.

Little attention has been given to extradural hematoma in the posterior fossa where the arterial supply of the dura is scanty. A clot forming between the dura and bone of the posterior fossa arises from a laceration of one of the dural sinuses.

A review of the literature fails to record any clinical discussion of these cases prior to McKenzie's<sup>1</sup> article in 1938. This writer describes such a case in a child recognized only at autopsy where an extradural clot measuring 2 cm. in thickness and 5 cm. in diameter was found over the right cerebellar hemisphere. He also relates the history of two adult patients, each of whom had extradural cerebellar collections of blood as extensions from extradural clots over the cerebral hemispheres. A posterior fossa operation was performed on one patient who died shortly afterward. The other patient had a temporal exploration and the posterior fossa clot was found at autopsy.

Lecount and Appelbach<sup>2</sup> in 1920 reporting on 504 autopsied cases of skull fracture had 8 cases of extradural hemorrhage in the posterior fossa. The source of hemorrhage in each instance was from one of the transverse sinuses and the clot did not exceed 50 Gm. Likewise, Vance<sup>3</sup> in 1927 recorded 512 autopsies of skull fracture and noted 4 cases of extradural hemorrhage from torn lateral venous sinuses. However, it was not clearly stated whether these clots were entirely confined to the posterior fossa or extended upward over the occipital lobes. Mayfield<sup>4</sup> recently had a patient in whom a cerebellar clot was suspected but who died before the posterior fossa could be explored. Autopsy revealed an extradural cerebellar hematoma.

The present case is reported in considerable detail because of the rarity of the condition, the fact that we found no reported case which

recovered, and to emphasize the features of a clinical picture which is highly suggestive of extradural hemorrhage in the posterior fossa. Careful study of the case led to a correct preoperative diagnosis and the appropriate operative procedure was followed by complete recovery of the patient.

**CASE REPORT.**—(No. 73891.) A previously healthy negro male, 9 years of age, was admitted to Saint Philip Hospital, Dec. 18, 1939, and discharged Jan. 3, 1940.

**Present Illness.**—Two days before admission the child fell from a moving truck, striking the back of his head, but was not rendered unconscious. Shortly afterward he was brought to the emergency room of the hospital where examination showed an alert and cooperative child, the only sign of injury being a small hematoma in the left occipital region. All reflexes were normal and the patient was discharged. He was returned in about twenty-four hours because of headache, some drowsiness, and because he had vomited once or twice. Again the neurological examination was essentially negative. The child was taken home and was brought to the hospital again the following night. This time he was moderately drowsy, occasionally very restless, complained of headache and had vomited several times. There were still no abnormal neurological findings. However, the patient was admitted to the hospital for observation. Fifteen hours later (morning of the third day following accident), the child was very drowsy but moved readily on painful stimulation. He would persistently lie on the left side and when turned on his back would again promptly turn to the left side.

On examination the hematoma in the left occipital region was still present. The neck was spastic and the patient cried out when attempts were made to flex it. The pupils were equal, moderately dilated and reacted to light. There was no nystagmus or strabismus. All cranial nerves were normal including the optic disks. The patient moved all extremities equally well, but there was definite generalized hypotonia. The biceps, triceps, knee and ankle jerks were now entirely absent. The Babinski sign was absent. The general physical examination was essentially normal. The blood Wassermann test was positive. X-ray examination of the skull in the anteroposterior view showed a long linear fracture extending from the lambdoidal suture downward into the foramen magnum in the midline (Fig. 1).

The child was now obviously seriously ill and an immediate operation seemed advisable. The operative site was largely determined by the sequence of events which had taken place since the accident. Briefly, the child was not stuporous but had been unconscious, the neck was spastic and passive motion was very painful. He invariably lay on the left side, hypotonia developed and later areflexia appeared. After these facts were established and knowing that a fracture of the occipital bone was present, it seemed most likely that a blood clot was present in the posterior fossa causing cerebellar compression and obstructive hydrocephalus.

**Operation (J. L. T.), Dec. 19, 1939.**—Under ether anesthesia, bilateral anterior parietal burr openings were made to rule out possible clots over the cerebral hemispheres. The left lateral ventricle was tapped and 30 c.c. of clear ventricular fluid was obtained under pressure. The needle was withdrawn without removing more fluid. The hydrocephalus gave added proof that an obstruction was present in the posterior fossa. Consequently, the patient was prepared for bilateral burr openings of the posterior fossa. An opening was made over the center of the right fossa and immediately about 10 c.c. of old, thin, dark blood escaped under marked pressure. An organized blood clot was readily visible beneath, necessitating an extension of the scalp incision in a bow-shaped outline and removing the bone over the right and left fossae in order to expose the hematoma (Fig. 2). The early



organized hematoma was then removed with suction and by pulling adherent portions away from the dura. The clot was at least 3 cm. thick near the midline and had compressed the midline structures and right cerebellar hemisphere considerably more than the left. An inspection of the borders of the hematoma showed that it had extended on the right, lateralward to the sigmoid sinus. Above, the dura enclosing the lateral sinus was stripped from the bone near the torcular, while on the left, the edge of the clot was near the sigmoid sinus, and below it had extended to the foramen magnum (Fig. 3). As a small portion of the clot was being pulled from

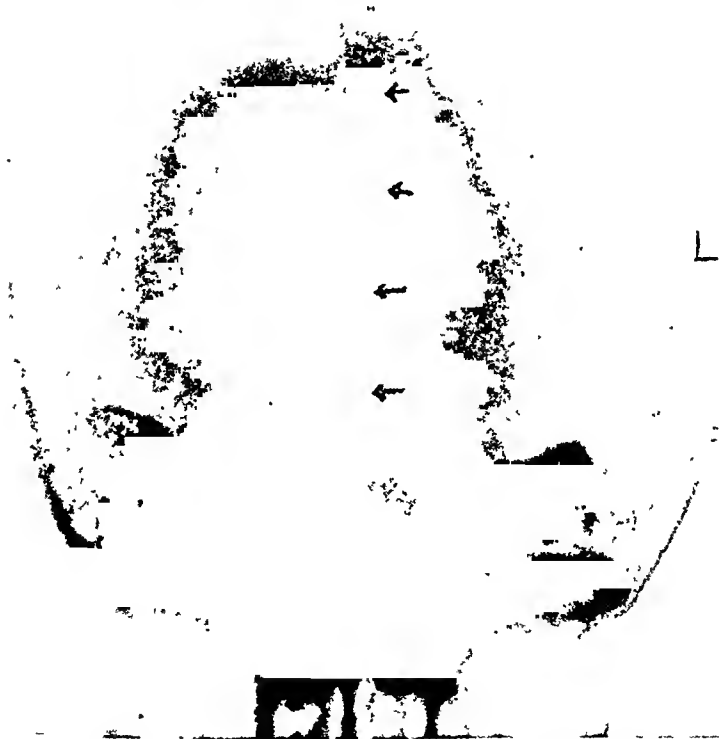


Fig. 1.—X-ray film showing long linear fracture from the inion to the posterior border of the foramen magnum in the occipital bone. Fracture line indicated by arrows.

the torcular, there was profuse bleeding which stopped upon releasing the tension. It was therefore concluded that the torcular Herophili had been torn when the skull was fractured and that the lacerated venous channel was the source of the hemorrhage. When all of the hematoma had been removed, the contents of the posterior fossa re-expanded and began pulsating. Immediately the noisy and irregular respiration became quiet and even. The wound was closed in layers with interrupted black silk. One rubber tissue drain was placed in the right extradural space and was removed twenty-four hours later.

The patient reacted promptly from the anesthesia and four hours later could talk coherently but was moderately drowsy. Improvement was continuously satisfactory so that he was up about the ward on the eleventh postoperative day. Examination showed that the wound had healed by primary intention. There was no stiffness of the neck. The cranial nerves were normal. There was normal muscular tone of the extremities. All of the deep and superficial reflexes were present, equal and normally active. The Babinski sign was absent. There was no ataxia. The child was discharged sixteen days after admission. When seen in the out patient department two weeks later the examination was negative and his mother stated that he seemed normal in all respects. The patient was last seen on Jan. 21, 1941. At that time he had no complaint, the neurological examination was negative, and he appeared to have no residual impairment.



Fig. 2.

Fig. 2.—Appearance of incision fifteen days after operation for evacuation of extradural hemorrhage from the posterior fossa.

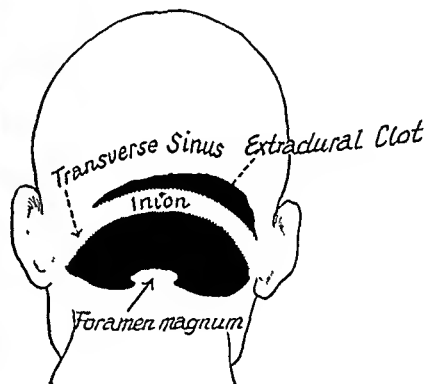


Fig. 3.

Fig. 3 —Diagrammatic view of the size and location of the clot in the posterior fossa.

The relatively slow onset of symptoms in this case, requiring more than sixty hours for drowsiness to appear, was caused by obstruction of the ventricular system by the slowly forming clot, rather than by direct pressure of the clot on the cerebellum. A hematoma from sinus origin forms slowly because the venous pressure within the sinus is only about 4 to 6 mm. of Hg. Since there are no large arterial vessels on the dural surface of the posterior fossa, it is safe to assume that all surgical clots in this region are of venous origin. Therefore, a rather long latent period, possibly in terms of days, may intervene between the time of injury and the onset of symptoms indicating the presence of a clot.

Before the diploe have formed in the skull of a child the dura is more tightly adherent to its inner surface than in an adult. Should a fracture line cross a venous sinus in the occipital fossa a tear in a sinus of

the tightly adherent dura may occur. The transient displacement of the bone fragments strips the dura from the bone, thus allowing extravasation of venous blood between the bone and dura. It seems unlikely that a tear in a sinus in this location can occur without a fracture of the skull. From reports in the literature and the experience of the present case, it may be said that a hematoma of the posterior fossa does not occur in the absence of skull fracture. It is difficult to say why patients with rapidly expanding lesions of the posterior fossa prefer to lie on one side, usually on the side of the lesion. A suggestion is that an attempt is being made to keep the weight of the clot off of the vestibular nuclei in the vermis and vagal nuclei in the brain stem, thereby preventing reflex vertigo and vomiting. This phenomenon of forced position has been observed on a number of occasions at this clinic. Some years ago a young boxer received a light blow on the back of his head and about twenty-four hours later became very drowsy. He would persistently lie on his side and when turned on his back would vomit violently and rapidly turn to the side again. At operation by one of us (C. C. C.) a large acute intracerebellar hematoma was removed and the patient made an uneventful recovery.

Frequent neurological examinations are necessary, to observe the appearance and progression of hypotonia and hyporeflexia which becomes evident as drowsiness increases. These cerebellar signs in the presence of nuchal rigidity are most important aids in making a correct diagnosis. Even though this type of lesion is extremely rare it should be considered in a drowsy patient who has evidence of cerebellar compression and a fracture of the occipital bone.

It is important to stress the fact that morphine should not be given or a lumbar puncture performed in the management of suspected extradural hemorrhage in the posterior fossa. Morphine notably suppresses respiration in the already drowsy patient and is dangerous when increased intracranial pressure is present. Morphine should never be given until the intracranial pressure has been controlled. Lumbar punctures may be helpful in the diagnosis of nonoperative cases of acute head injury, but the procedure is definitely contraindicated if an extradural hemorrhage is suspected, because sudden disturbance of intracranial relations by withdrawing cerebrospinal fluid may cause a shift of or pressure upon the brain stem with damage to important centers. Since the primary effect of an acute extradural hemorrhage is to produce increased intracranial pressure and since bloody spinal fluid does not definitely rule out such a clot, one easily realizes that lumbar puncture adds little information to the history and neurological examination.

The diagnostic criteria for recognition of an extradural hematoma in the posterior fossa are as follows: There is a history of a blow on the back of the head severe enough to produce a fracture of the skull but

which may or may not cause unconsciousness. This is followed by headache of gradual increasing severity and is usually accompanied by nausea and vomiting. Drowsiness and restlessness appear and progress until the patient lapses into unconsciousness. However, during the drowsy state several things may be noted. The patient prefers to lie on one side and will promptly return to the same side when placed on his back. Nuchal rigidity develops, nystagmus may or may not be present, and the deep reflexes disappear. As unconsciousness deepens, generalized hypotonia develops, the pulse and respiration become irregular and death is imminent unless there is prompt surgical intervention with removal of the clot.

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# EXPERIMENTAL STUDIES ON ALIMENTARY AZOTEMIA

## II. THE RELATIVE IMPORTANCE OF THE PLASMA AND ERYTHROCYTE FRACTIONS OF ABSORBED BLOOD\*

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THE occurrence of an increased blood urea nitrogen concentration in certain cases of intestinal hemorrhage, particularly in patients with bleeding peptic ulcer, has considerable prognostic significance. In previous papers,<sup>1, 2, 3</sup> the literature was reviewed on this subject of azotemia following gastrointestinal hemorrhage in patients and in experimental animals and the term alimentary azotemia was introduced as a more definitive name for this condition and one comparable to those applied to other similar processes. This earlier work agreed closely with that of Schiff and associates<sup>4</sup> and with slight variations with that of Kaump and Parsons.<sup>5</sup>

Most observations on human patients and experimental work on animals so far reported have employed the use of whole blood in the study of alimentary azotemia. Schiff and co-workers<sup>4</sup> observed an appreciable degree of alimentary azotemia in one human subject following the ingestion of 1.8 kg. of lean meat. That the cells rather than the plasma are the active principle in producing this type of azotemia was first stated in preliminary reports by one of us (C. F. C.)<sup>6</sup> in 1940, and later by the other (H. N. H.)<sup>7</sup> and by Boals and both of us<sup>8</sup> in 1940. In a later paper, Yuile and Hawkins<sup>9</sup> in 1941 reported independent data confirming this conclusion.

In consideration of this and other observations made in our earlier experiments, it occurred to us that the etiology of alimentary azotemia should be further studied by breaking the whole blood down into its component parts to determine if possible which fraction or combination of fractions was responsible for the production of alimentary azotemia.

### EXPERIMENTAL

*Method.*—A large quantity of citrated beef blood was separated into the plasma and cell fractions by centrifuging. Five dogs were given varying amounts of beef cells by stomach tube and five dogs were given beef plasma in the same manner. The dogs were young, healthy, and apparently free from renal disease.

Urea nitrogen determinations, using essentially the same method as that of Van Slyke and Cullen,<sup>10</sup> were made from samples taken at 2:00

\*A portion of the thesis submitted by C. Frank Chunn to the Graduate School of the University of Michigan in partial fulfillment of the requirements for the Degree of Master of Science in Surgery.

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and 8:00 A.M., 12:00 noon, and at 4:00 and 8:00 P.M. Blood was drawn for analysis from the jugular vein of each dog during a control period of from one to three days preceding each series of experiments and continued twenty-four hours after the curve had returned to normal. The dogs were given their usual amount of food divided into four small feedings daily. Water was given freely. As in our previous experiments on the effects of whole blood, when the normal blood urea nitrogen curve was established, the dogs in Group A were given beef blood cells by stomach tube in divided doses at intervals and the dogs in Group B were similarly given beef plasma.

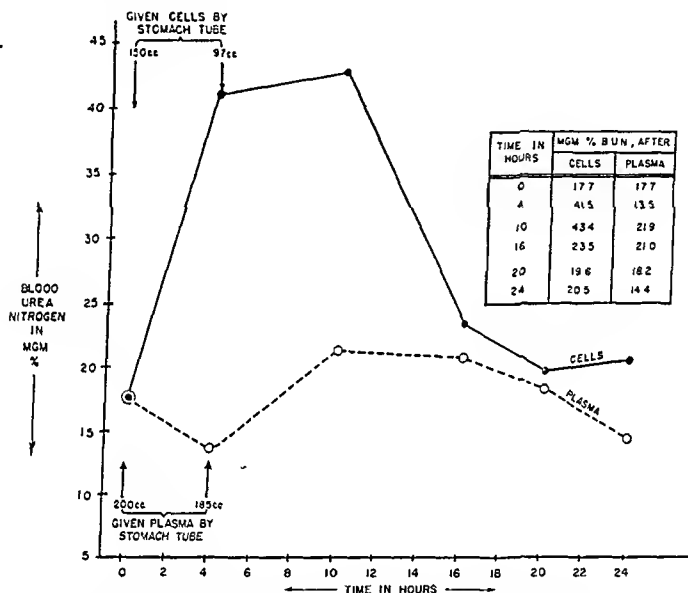


Fig. 1.—The comparative effects of blood cells and blood plasma in the production of alimentary azotemia in dogs.

*Results: Relative Effects of Plasma and of Red Blood Cells.*—The five dogs receiving the beef blood cells all showed an elevation of blood urea nitrogen above normal within four hours and a maximum concentration of blood urea nitrogen at various intervals between five and twelve hours, depending on the amount and number of doses given. After administration of the last dose of cells, the return to normal of the blood urea nitrogen required from twelve to seventeen hours as seen in Fig. 1 which represents the result in a typical experiment.

The five dogs that received beef plasma by stomach tube showed a longer interval between the first administration of plasma and the initial rise of blood urea nitrogen. The rise occurred in four experiments at four, eight, ten, and eleven hours respectively. In one dog receiving plasma there was no deviation from the normal blood urea nitrogen curve throughout the experiment. The maximum blood urea nitrogen concentration was apparent in the four dogs which showed a rise at

intervals of from eight to eleven hours, one dog showing no elevation as mentioned. The return of the blood urea nitrogen to normal following the last administration of plasma required from five and one-half to twenty hours as shown also in Fig. 1.

It was noted that with the exception of a small portion of the curves of Dogs 3 and 5 (not shown in Fig. 1) the blood urea nitrogen was always higher for the animals receiving blood cells than for the animals receiving blood plasma. This occurred even when the doses of plasma were double that of cells. In one experiment where the maximum concentration of blood urea nitrogen of the plasma-fed dog attained the same elevation as that of the cell-fed dog on the first day only, a total of only 371 c.c. of blood cells was given as compared to 489 c.c. of blood plasma preceding the maximum elevation of blood urea nitrogen. In the other experiment where the blood urea nitrogen elevation persisted a little longer in the plasma-fed animal, the dosage of plasma was 700 c.c. as compared to only 395 c.c. of cells. The other three experiments revealed a much lower blood urea nitrogen concentration for the animals given plasma, and as mentioned before, in one experiment, there was no elevation even though the animal was given 600 c.c. of plasma in 200 c.c. doses at four-hour intervals.

*Additional Experiments on Rats.*—Deviating from our usual procedure, two adult albino rats weighing from 350 to 400 Gm. were given 15 c.c. of blood cells by stomach tube and at the same time 15 c.c. of physiologic saline solution intraperitoneally to combat any possible degree of dehydration. Three control rats received only the 15 c.c. of saline solution intraperitoneally. A control rat was killed at this time and 3 c.c. of blood taken from the heart showed a blood urea nitrogen of 14.7 mg. per cent. Six hours later a blood cell-fed rat was killed and 3 c.c. of heart blood recovered. The blood urea nitrogen was 47.6 mg. per cent, and the control at this time revealed a blood urea nitrogen concentration of 13.4 mg. per cent. This was repeated with the second experimental rat in eighteen hours, at which time the blood urea nitrogen was 29.8 mg. per cent, as seen in Fig. 2.

*Effect of Ingested Blood on Rectal Temperature and General Condition.*—Rectal temperatures were taken on two dogs five times daily; i.e., 2:00 and 8:00 A.M., 12:00 noon, and 4:00 and 8:00 P.M. No elevation beyond the normal diurnal variation occurred following administration of beef blood cells and beef blood plasma. However, the dogs did appear to be sick and would lie listlessly in their cages. Their food consumption per day was somewhat diminished, but the fluid intake was usually increased after the administration of blood, cells, or plasma.

#### COMMENT

From the evaluation of our experiments on azotemia following intragastric administration of whole citrated beef blood, beef blood cells, and beef blood plasma, it would seem that blood in the gastrointestinal tract

undoubtedly causes an appreciable degree of azotemia. It would also seem that blood cells play the major role in producing azotemia, and that the degree of azotemia is directly proportional to the amount of blood, cells, or plasma put into the gastrointestinal tract.

Of the ingested materials used, i.e., whole blood, blood cells, and blood plasma, the average amount of hemoglobin in the whole blood was 11.65 Gm. per 100 c.c. as shown in Table I, and the average total plasma protein of blood was 4.74 Gm. per 100 c.c. Furthermore, the average hemoglobin content of blood cells was 29.36 Gm. per 100 c.c. as shown in Table I. These figures represent actual amounts of protein per 100 c.c. In other words, 29.36 Gm. hemoglobin per 100 c.c. for blood cells equals 29.36 Gm. of protein per 100 c.c. Hemoglobin is a protein containing iron and classified as a histone. These facts are suggestive that the azotemia was caused simply by the absorption of protein from the gastrointestinal tract with resultant urea formation in the liver from the absorbed protein. In these experiments, therefore, the chief cause of the increased blood urea nitrogen would not seem to be shock, hemorrhage, hypochloremia, decreased renal function, dehydration, increased body protein catabolism or shock, as shown in Table II.

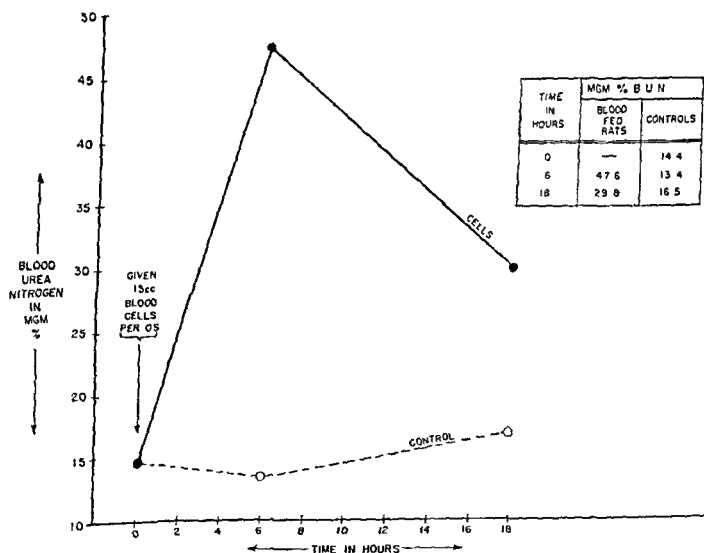


Fig. 2.—The effect of feeding red blood cells in the production of alimentary azotemia in the white rat.

*Effect of Hemoglobin.*—To carry this aspect of the investigation further, another experiment was performed using two dogs. One dog was given 60 Gm. of pure hemoglobin in two 30 Gm. doses four hours apart. The second dog received 100 Gm. of pure hemoglobin in one 60 Gm. and one 40 Gm. dose four hours apart. As is seen in Fig. 3, both dogs showed an initial increase in blood urea nitrogen in four hours, a



TABLE I  
ANALYSIS OF SPECIMENS USED IN THESE EXPERIMENTS

SPECIMEN NO.	HEMOGLOBIN (GM. %)	HEMATOCRIT (%)	UREA NITROGEN (MG. %)	TOTAL PLASMA PROTEIN (GM. %)
<i>Whole Beef Blood</i>				
1	11.0	33	19.1	4.3
2	12.6	35	9.9	5.0
3	13.0	37	17.7	5.2
4	10.0	36	16.1	4.5
5	—	—	16.9	—
Average	11.7	35	15.9	4.7
<i>Beef Red Cells</i>				
1	28.5	—	19.1	—
2	28.4	—	10.7	—
3	31.2	—	13.9	—
Average	29.4	—	14.6	—
<i>Beef Plasma</i>				
1	—	—	9.1	4.3
2	—	—	15.5	5.0
3	—	—	14.4	5.2
4	—	—	—	4.5
Average	—	—	13.0	4.7

maximum concentration of blood urea nitrogen in twelve hours, and a return to normal in twenty-eight hours. Furthermore, the dog receiving the larger dose of hemoglobin showed consistently higher blood urea nitrogen concentrations, leading one to believe that the degree of azotemia was due to and directly proportional to the amount of ingested hemoglobin.

*Effect of Protein.*—Following this observation two dogs were given a single large protein meal consisting of casein and ground beef, the first dog receiving 83 Gm. of protein, and the second 175 Gm. The same type of azotemia curve was obtained as for whole blood, cells and hemoglobin. The initial elevation of blood urea nitrogen appeared in one hour with a maximum concentration in five hours and a return to normal in twenty-five hours. Here again as shown in Fig. 4, the curves parallel

TABLE II  
AZOTEMIA, POSSIBLE CAUSATIVE FACTORS AND CLASSIFICATION\*

I. Renal
II. Extrarenal
1. Shock
2. Hemorrhage
3. Hepatorenal
4. Dehydration
5. Starvation
6. Increased body protein catabolism
7. Hypochloremia
8. Alimentary absorption

\*Combinations may be frequent, thus shock may elevate the blood urea nitrogen by means of renal impairment, etc.

each other with the blood urea nitrogen curve of the dog receiving the larger dose of protein consistently several milligrams per cent above the other until normal is approached. That the protein in the cellular hemoglobin is the active element is corroborated by the results of Yuile and Hawkins<sup>17</sup> (1941). These authors have shown in an excellent presentation that the blood urea nitrogen rise following the injection of various substances is quantitatively proportional to their protein content.

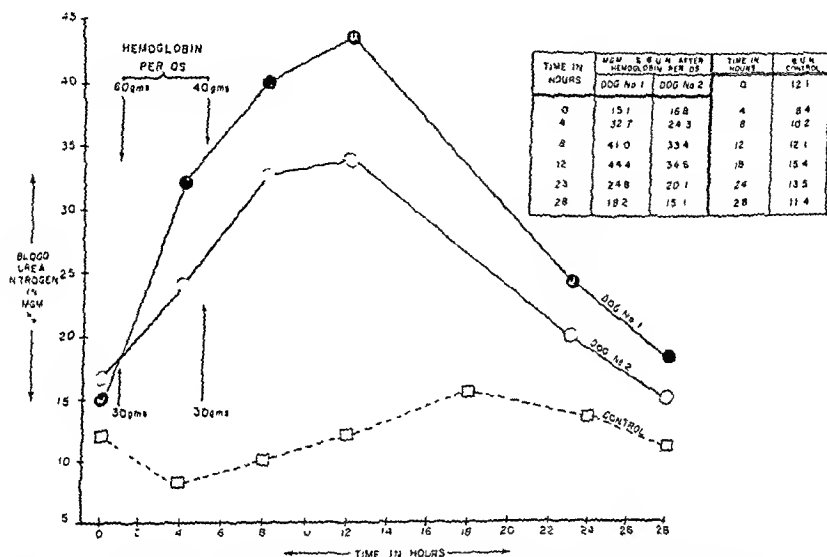


Fig. 3.—The effect of hemoglobin in the production of alimentary azotemia in dogs.

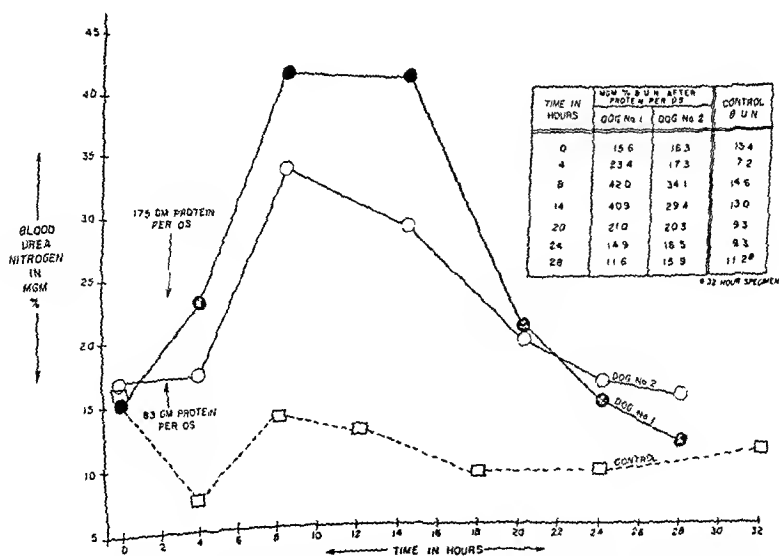


Fig. 4.—The effect of protein in the production of alimentary azotemia in dogs.

*Effect of Iron.*—Two dogs were given approximately 1 Gm. of iron each by stomach tube in the form of 10 per cent iron ammonium citrate solution. The blood urea nitrogen curves were quite flat one and two days later, showing no azotemia following administration of rather large doses of iron (1 Gm. of iron is the amount normally present in 1,000 c.c. of human blood<sup>11</sup>).

*Effect of Urea.*—It is well known that urea given by mouth will increase the blood urea content. The possibility arises therefore that the urea contained in red blood cells might explain their greater effect in production of alimentary azotemia as compared to plasma. Comparison of the figures represented in Table I readily dispels this idea. It is seen that the average urea nitrogen content of beef plasma is 13 mg. per cent, while that of beef red cells is only 14.6 mg. per cent, an inappreciable difference.

#### SUMMARY

The intragastric administration of citrated beef blood cells in five experiments revealed an initial elevation of blood urea nitrogen within four hours and a maximum concentration between five and twelve hours (depending on the amount and number of doses given) with a return to normal in twelve to seventeen hours following the last administration of cells.

Five dogs were given varying amounts of beef plasma into the stomach. Four of these revealed an initial elevation of blood urea nitrogen between four and eleven hours, a maximum concentration between eight and eleven hours (depending on the amount and number of doses given) with return to normal levels in five and one-half to twenty hours following the last administration of plasma. One dog revealed no elevation above normal. The average degree of azotemia attained for plasma-fed dogs was much less than that of the cell-fed dogs.

A comparable curve was obtained in white rats following administration of blood cells into the stomach.

Two dogs were fed 60 and 100 Gm. of pure hemoglobin respectively. Both showed an initial elevation of blood urea nitrogen in four hours, a maximum elevation in twelve hours, and a return to normal in twenty-eight hours.

Two dogs were fed large protein meals and showed an initial elevation of blood urea nitrogen in one hour, a maximum concentration in five hours, and a return to normal in twenty-five hours.

Blood urea nitrogen values were not elevated in two dogs given 1 Gm. of iron (10 per cent iron ammonium citrate) each by stomach tube.

Analysis of the blood cells and blood plasma used indicated that the greater activity of cells in comparison to plasma in producing a rise of blood urea nitrogen could not be explained by an excess of urea inherent in the cells.

## CONCLUSIONS

1. Alimentary azotemia seems to be due to the red cell element of blood to a greater degree than to the plasma fraction.
2. Since marked rises in blood urea nitrogen were also obtained following ingestion of hemoglobin and protein, the rise caused by ingested blood probably is due to and to a large extent proportional to the resultant absorption of protein from the gastrointestinal tract.
3. The ingestion of iron in large amounts was found not to produce alimentary azotemia.

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## REPAIR OF THE LARGE UMBILICAL HERNIA

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THE surgical treatment of the umbilical hernia depends upon its size. The umbilical hernia possessing a small sac is usually found in the young and thin, is surrounded by excellent fascia and offers no problems to the operator since it can be easily repaired by any number of simple methods with excellent end results. We are concerned in this paper with the large umbilical hernia which occurs in older and obese people, has relatively poor contiguous fascial structures, and is apt to recur in over 10 per cent of the cases when the best type of operation is performed.

The small umbilical hernia was adequately controlled even before the time of Celsus by reduction and simple forms of trussing. The larger types were always difficult to reduce and even less amenable to binding until Lucas-Champonnière in 1881<sup>1</sup> successfully executed the open operation by overlapping the lateral edges of the rectus fascia. Eighteen years later William J. Mayo<sup>2</sup> suggested the transverse overlapping of the fascial flaps and this procedure is today recognized as most satisfactory. The incidence of over 10 per cent recurrence<sup>3</sup> using the Mayo technique has led us to develop a modification which obviates certain known faults.

The umbilical hernia starts as an outpouching through the weak area at the upper angle of the umbilicus at the site of the obliterated omphalomesenteric vein. The vectors of force at this point are outward and downward and as the pouch increases in size, the bowel and omentum insinuate through the neck and push the lateral edges of the recti outward. Since in the large hernia the rectus muscle cannot be brought to the midline, the repair can only make use of the contiguous fascia. The transverse overlapping is recognized as an excellent procedure in strengthening the fascial closure, but what has not been suggested in the past is the possibility that the abdominal contents following the vectors of force may be insinuated between the flaps if the method of Mayo is used. We have imbricated our flaps in a manner exactly opposite that of the Mayo method by placing the upper flap posterior to the lower flap as seen in Fig. 1. The second weak spot in the Mayo repair is at the lateral angle. When one imbricates two straight fascial edges, one finds that either the lateral angles are not overlapped or an oblique tunnel is formed at either angle. This fault was recognized by Stone<sup>4</sup> and corrected by a method of plication which, however, did not overlap the

first fascial layer. By curving the lateral angles upward we have produced a convex upper flap and a concave lower flap that permit overlapping at all points, prevent tunnel formation at the angles, and do not introduce further weakening areas of the wall.

#### OPERATION

A transverse elliptical incision is made about the umbilicus extending through the skin and subcutaneous tissue to the aponeurosis of the rectus. The fascia is then cleaned for a distance about the neck of the sac and the sac entered. With a finger in the peritoneal cavity, the sac is completely excised together with overlying skin. The contents of the sac are reduced and repair follows. If the neck of the sac has not been enlarged during taxis of the hernial contents, it is now done, the incision being

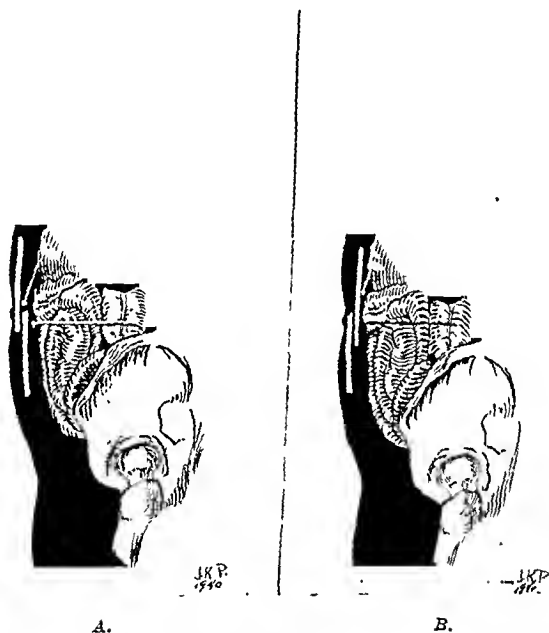


Fig. 1.—A. In the Mayo umbilical hernioplasty the vectors of intra-abdominal force (indicated by arrows) allow insinuation of contents between the fascial leaves. B. Modified technique shows lower fascial flap anterior to upper flap with no insinuation of intra-abdominal contents possible.

extended at the angles, cutting in an upward curve for a distance of 5 to 6 cm. This distance may be increased without weakening the wall. The flaps having been cleaned of fat and connective tissue, the upper flap is placed posterior to the lower flap and interrupted sutures of E silk inserted, the needle being passed through the lower flap from without inward, then through the upper flap in mattress fashion and back through the lower flap from within outward. (Fig. 2.) No attempt is made to close peritoneum separately, the suture traversing both rectus fascia and peritoneum. The sutures are placed at 2 cm. intervals and all are inserted before the knots are secured. The overlapping or re-

dundant edge of the lower fascial flap is then sutured to the upper rectus fascia with interrupted E silk. No sutures are placed in the subcutaneous layer and the skin is closed with fine silk. In cases of marked obesity a small stab wound is made lateral and dependent to the incision and a rubber dam drain inserted.

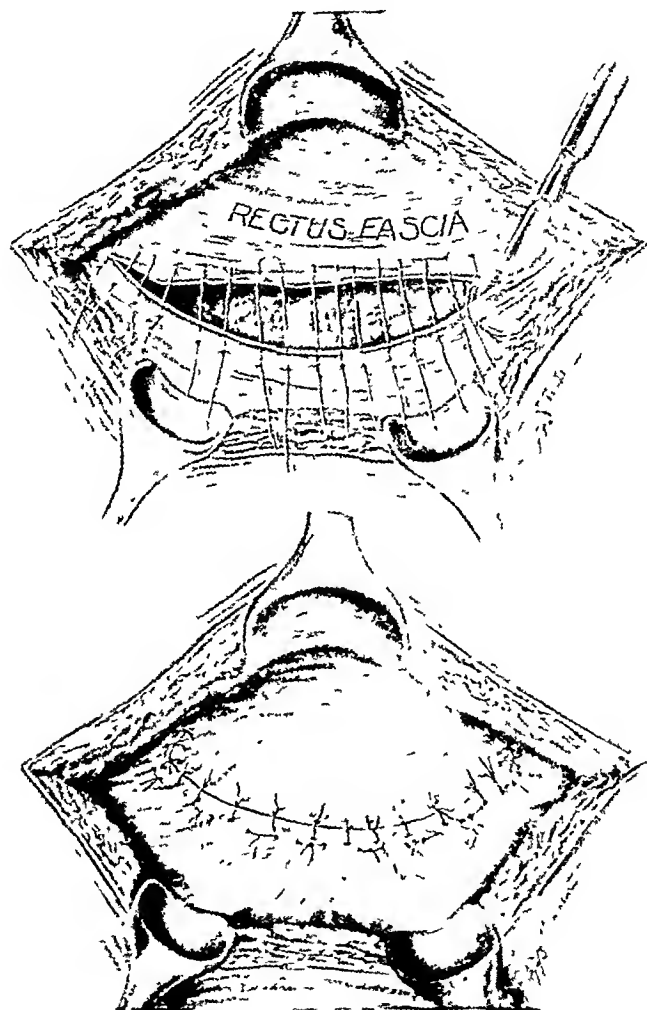


Fig. 2—1. Scar has been removed and neck enlarged by extension of the incision in a curve upward at the angles. A convex upper flap and a concave lower flap are shown as result of this extension. Interrupted sutures are placed, bringing lower flap above upper flap. B. Repair completed by suturing redundant fascial flap to upper flap.

#### COMMENT

We suggest a modification of the Mayo operation because its use has been attended by a moderately high percentage of recurrences in the hands of skilled surgeons. There are two definite weaknesses in the Mayo repair which can be prevented. The first is responsible for re-

currences at the central portion of the incision and is due to insinuation of abdominal contents between the imbricated fascial leaves. The second weak area is at the lateral angle and is due to overlapping of straight fascial edges. The operation described above strengthens the central weak area, prevents insinuation of abdominal contents through the fascial leaves, overcomes the weak imbrication at the angles, and prevents tunnel formation. It can be used in all types of umbilical hernias but is recommended only for the large adult cases since the small hernia can be cured with less radical surgery.

#### CONCLUSIONS

Modification of the Mayo operation for large umbilical hernia is suggested.

Reurrences at the central portion of the repair are probably due to insinuated contents through fascial layers and are here obviated by placing the lower flap anterior to the upper flap.

Reurrences at the lateral angles may be due to faulty imbrication of straight fascial edges and are here remedied by using curved fascial flaps.

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# Editorial

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## A "New" Polio Treatment

ONCE AGAIN the popular press has grasped a spectacular piece of medical news and greatly distorted it. The saga of Sister Kenny of Australia and her polio cure, which was first discussed in medical journals in 1938, has now reached the *Hearst American Weekly* (Aug. 17, 1941) where medical men are characteristically flayed for their needless conservatism and inordinate ignorance. Her empiric methods of hot packs and muscle training are described as likely to revolutionize the treatment of poliomyelitis and to effect cures in more than half the cases treated.

Careful statistical studies of Sister Kenny's methods have been undertaken by Wallace Cole and his associates at the University of Minnesota, and from these it can be determined whether this "abandonment of immobilization" is of any real value or not.<sup>1</sup> Nevertheless until the Minneapolis investigators submit their final report this entire question must remain unsettled.

That others devised similar therapeutic methods long ago is well illustrated in a forthcoming history of medicine in Texas,<sup>2</sup> wherein Elena Zamora of south Texas describes her father's cure:

"When a young boy (in the 1850's) Porfirio Zamora and other members of the little settlement along the Rio Grande were stricken with 'El Tullidor,' thecrippler, as they called it. My father survived, but was left with arms and legs entirely paralyzed. He had no strength in his neck to keep him erect so he had to lie in bed all the time. One day an Indian from the Toleha tribes, around what is now Laredo, told my mother that one of the Indian chiefs of that tribe could cure victims of 'El Tullidor.' Grandmother knew it was a long and tedious journey to Las Lajas, the Indian encampment there. Preparations were made and the cavalcade departed. They went in ox carts escorted by men on horseback. When they arrived at Las Lajas they were given a large cabin by the Chief, Juan Castro. He told Grandmother that he was going to try to cure her son . . . and that he was to have entire control of the boy. Grandmother was willing to do anything that would restore her son to normalcy.

"A trough long enough for father to rest in comfortably was built at the chief's orders. Then the cure began. Each morning he was taken to the sands and allowed to lie there while two men, who took charge of him, rolled him over the hot sands and covered him with them. He

was then taken into the cabin and dipped into the trough filled with goat's milk. This milk was kept as hot as it was possible, by drawing off quantities of it and replacing them with hot milk. All the time he was in the milk trough he was being massaged and his joints moved constantly. This treatment lasted for almost an hour. He was then bathed in warm clean water and put to bed. . . . He was left alone till late in the evening when he was again massaged, but this time it was with a salve made from goat marrow and pungent herb. . . . At bed time he was given another treatment. Every joint in his body was covered with a poultice made from ground corn, goat milk, and oil from the marrow of bones. These poultices were kept warm by dropping warm oil on the covers. He slept with these bandages on. The treatment continued for many days. He felt as if his whole skin was raw, but not uncomfortable. Every night before being left with Grandmother for the night he was given . . . a tea brewed from herbs and a small quantity of Mescal.

"One night father awoke and felt a very pronounced desire to scratch a certain place on his neck. . . . Suddenly his fingers moved, he tried to raise his hand and it responded, and slowly but surely, he reached the itchy spot on his neck and scratched it to his heart's content. . . . He tried the other hand, it moved also, but not as freely. He turned his neck and it responded. He wriggled his toes, moved his legs, and then he began to cry, returning thanks to God and the Old Indian. . . .

"It was not long before he was able to sit up, then stand and practice a few steps. All the while the treatments continued. At last he was well, his limbs began to fill out, he could walk for several minutes without aid. The miracle had been performed. . . ."

Thus old Chief Juan Castro living in the lower Rio Grande Valley 100 years ago anticipated the routine devised by Sister Kenny in the Australian Bush, and as the record shows cured at least one patient. Perhaps if physiotherapy methods in poliomyelitis are to be profoundly altered and our concepts of treatment revolutionized, the new therapy should properly be called the Juan Castro-Sister Kenny treatment for poliomyelitis.

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San Antonio, Tex.

# Recent Advances in Surgery

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CONDUCTED BY ALFRED BLALOCK, M.D.

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## RECENT PROGRESS IN THE SURGICAL TREATMENT OF LUNG TUMORS

W. E. ADAMS, M.D., CHICAGO, ILL.

*(From the Department of Surgery of the University of Chicago)*

*(Continued from the November issue)*

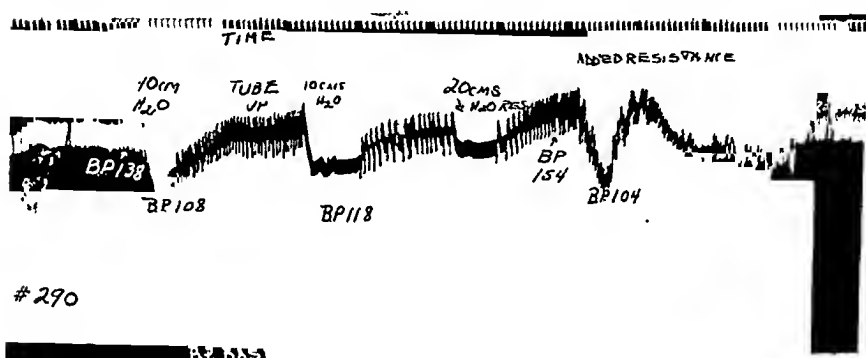
### TREATMENT

Until within recent years, surgical extirpation of lung tissue for carcinoma was attended by so great a risk that most lung tumors were treated either by bronchoscopic removal or by deep x-ray. After years of investigation, treating hundreds of patients by this method, it has become generally believed and more recently quite definitely proved that bronchogenic carcinoma has not been cured by x-ray therapy.<sup>23, 53</sup> In a recent communication Steiner<sup>54</sup> reports the results of x-ray treatment and its histologic effects on both the primary growth and the metastatic lesions. In no patient was a cure effected and survival was not noticeably prolonged by the irradiation.

Surgical treatment has been carried out sporadically for several decades. In 1912 a monograph on the subject was published by Adler,<sup>55</sup> who states: "There is every reason to hope that the technique of this new branch of surgery will be still further developed and that in the near future thoracotomy and operations on the lungs will be attended by no more risk than peritoneal operations today. If this is so, a new and great responsibility is placed upon the shoulders of internal medicine. It will be necessary, not only to educate the opinion of the laity so as to induce them to submit to these operations with the same readiness with which they now submit to peritoneal operations, but it will also be the sacred duty of the physician to recognize these cases and to recognize them as early as possible. When all the means of diagnosis outlined in this little study fail, where there is suspicion of tumor, but no assurance is possible, there should be—it is emphatically here stated—as little hesitation is resorting to an exploratory thoracotomy as there is now in submitting to an exploratory laparotomy." Adler's prediction has in substance come true and when his suggestions are followed beneficial results from surgery can be expected.

*Anesthesia.*—As has been previously stated, alteration of intrathoracic pressures with its deleterious effects on cardiorespiratory function has

been an important factor in the delay of progress made in intrathoracic surgery in general. Anesthesia is naturally very closely associated with the problem of preventing these deleterious effects. The maintenance of sufficient lung function during a surgical pneumothorax is of paramount importance to the success of the operation. The principle of the negative pressure chamber, as well as that of the positive pressure anesthesia technique originally administered by means of an intratracheal catheter has been applied to overcome this hazard. Intratracheal positive pressure anesthesia has enjoyed much success in performing this function. "Controlled respiration" without voluntary respiratory effort on the part of the patient may be obtained by the



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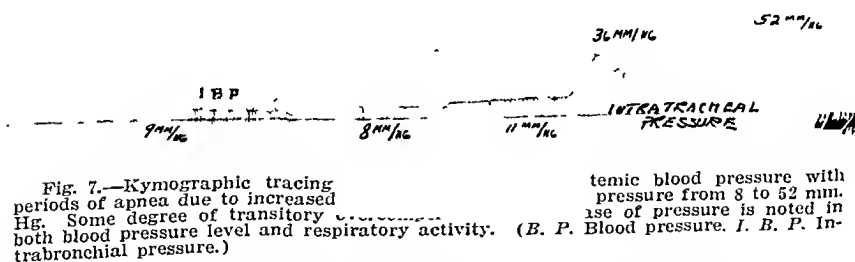


Fig. 7.—Kymographic tracing periods of apnea due to increased Hg. Some degree of transitory apnea both blood pressure level and respiratory activity. (B. P. Blood pressure. I. B. P. Intratracheal pressure.)

use of the proper mixtures of anesthetic agents administered under certain pressures. It also prevents suffocation by spasm of the glottis and, furthermore, allows for the aspiration of mucus and pus from the tracheobronchial tree, both during and at the termination of surgery. Because of its obvious usefulness, intratracheal positive pressure anesthesia has been widely accepted, and without sufficient attention being given to possible hazards or disadvantages. That these are present and may lead to disastrous results is evidenced by the reports of Stephens,<sup>56</sup> Bradshaw,<sup>57</sup> Bourne,<sup>58</sup> and Heidrick and co-workers.<sup>59</sup>

Elsberg<sup>11</sup> is usually credited with having performed the first thoracic operation using intratracheal insufflation anesthesia and in 1911 reported more than one hundred cases with very satisfactory results.

Little investigative work has been reported on the deleterious effects of positive intrabronchial pressure on the cardiorespiratory function in general, and on the parenchyma of the lung in particular. Macklin<sup>60, 61</sup> produced mediastinal emphysema and pneumothorax following overdistention of an isolated portion of the lung in cats. He demonstrated interstitial emphysema about the vascular tree of the lung with air progressing toward the hilum and into the mediastinum, and reasoned that the pneumothorax was secondary to the emphysema. Pressures employed in his studies varied from 10 to 200 mm. of mercury. His findings were substantiated by Marcotte and his associates<sup>62</sup> in our laboratory, the intrabronchial pressures necessary for the production of mediastinal emphysema being determined. A study of the alteration of the arterial blood pressure was also made at the same time. Briefly, it was found that in the dog a routine fall in the systemic arterial blood pressure of 8 to 10 mm. of mercury resulted from an elevation in intrabronchial pressure of 6 mm. of mercury. Intrabronchial pressures of 24 mm. of mercury or above were routinely accompanied by the development of mediastinal emphysema. The latter effect was produced in cats with only 20 mm. of mercury.

That such deleterious effects occasionally occur from the clinical use of intratracheal positive pressure anesthesia is seen in reports by Bradshaw, Heidrick, and others as above stated. These findings do not necessarily indicate that positive pressure anesthesia should be abolished but that minimal pressures should be used and that one should be cognizant of such deleterious effects of high pressures.

That positive pressure anesthesia is not always a prerequisite for intrathoracic surgery is demonstrated by the use of spinal anesthesia, a method which has been extensively employed with satisfactory results by surgeons both in Canada and England. T. Edwards<sup>16</sup> reported the use of percaine (1:1,500) with consistent anesthesia up to the level of the third dorsal segment maintained for well over two hours. He stated that the "advantages of cutting off nerve impulses arising from separation of dense adhesions between lung and chest wall and thereby limiting shock are obvious and although it is common to see a preliminary fall in blood pressure due to the anesthetic to rise during the later stages of the operation, when the operative effects should be appearing." When spinal anesthesia is used and cough produces respiratory distress, damage is "controlled by the administration of a little oxygen given under light positive pressure, with a firm-fitting face piece."

In the United States, surgeons have usually preferred general anesthesia using cyclopropane or ethylene-oxygen mixtures. Although intratracheal catheter administration has been widely employed, an ever-increasing number of surgeons have discontinued its use because of the

likelihood of introduction of infectious material from the mouth into the lower respiratory air passages or of injuring the mucous membrane of the tracheobronchial tree with subsequent inflammatory changes.<sup>47, 64-66</sup> We have found ethylene-oxygen administered through a snug-fitting face piece a very satisfactory anesthesia for various types of intrathoracic operations.

In conclusion, one may say that the simplest type of anesthesia, unhindered by complicating apparatus or traumatizing procedures in which minimal positive pressure is possible, is the anesthetic of choice. The method should facilitate good exposure, provide adequate oxygenation and support to respiration, necessitate minimal motion of the lungs with least interference of cardiorespiratory function, be nonirritating to the respiratory passages and minimize postoperative complications.

#### PREOPERATIVE PREPARATION

Preoperative preparation should include both local and general measures that best fit the patient for the alteration in cardiorespiratory function both during and following the surgical procedure. Not infrequently, a blood transfusion is necessary because of the existing anemia. Cross-matching for further transfusion either during or possibly following operation is also an essential procedure. Careful check-up of the cardiovascular system will lower the incidence of postoperative shock and cardiac failure. The question of preoperative digitalization as yet has been unsettled but may prove of definite value in certain individuals.

Where the necessity of total pneumonectomy is obvious, preliminary pneumothorax has several advantages. It not only gives information regarding the presence of adhesions between the lung and chest wall, as well as some of the characteristics of the existing tumor, but prepares the patient for cardiorespiratory function using only one lung following the operative procedure. By reducing the lung function slowly over a period of several days, the shock is thought to be much less severe than when the procedure is accomplished suddenly during the operation. The reduction in size of the lung to be removed is also of some advantage at the time of operation.

Rienhoff<sup>67</sup> has advised the use of beef broth for the production of granulations lining the pleural space prior to operation. This is accomplished by the use of 50 c.c. of beef broth bouillon introduced into the pleural cavity following the induction of pneumothorax. An effusion is produced which increases for approximately two days with polymorphonuclear leucocytes predominating. Within five to seven days the predominant cell is changed as the lymphocytes increase. The object of this procedure is to prepare a defensive wall against infection of the pleural space following surgery. This procedure as yet has not been widely used but may have value where few or no adhesions exist between the lung and chest wall.

## THE QUESTION OF OPERABILITY

Contraindications to operation may be directed toward the general condition of the patient or to local or metastatic involvement by the tumor. If the cardiovascular system is obviously markedly below par or if other degenerative changes have produced considerable debilitation, it is obviously unwise to subject the patient to such a major operation as pneumonectomy. Since the mortality of bronchogenic carcinoma has been practically 100 per cent without surgical intervention, many patients have been treated by resection of the involved lung where little hope was entertained for a permanent cure. With increasing experience, however, many of these hopeless conditions became obvious when exploratory laparotomy was performed, thus helping to prevent the operation from falling into disrepute.

As in the case of malignant tumors elsewhere in the body, obvious metastases contraindicate surgical intervention. When signs, symptoms, and diagnostic methods reveal no evidence of metastatic involvement, an exploratory thoracotomy is indicated. Considerable discussion regarding the presence of mediastinal glandular involvement as being a contraindication to surgery has not led to a universal agreement. It is known however that tumor-bearing lymph nodes may be removed together with the involved lung and the patient remain healthy and active without evidence of recurrence or metastatic involvement for some time.<sup>68\*</sup> This question will probably be better answered as more experience is gained in the handling of the tumor.

## OPERATION

The earlier operations performed for primary lung tumors consisted chiefly of the removal of one lung lobe or a portion of a lobe. Subsequent observations revealed that recurrence of the tumor or continuation of growth of the metastases was apt to result in a high percentage of patients where this was carried out. The operation of choice, therefore, was found to be a total pneumonectomy with resection of the mediastinal lymph nodes. More recently, a two-stage pneumonectomy has been devised and carried out by Rienhoff<sup>69</sup> in this country and by Edwards<sup>70</sup> in England. This procedure has been reserved more especially for older or poor-risk patients in whom the one-stage operation is too dangerous. In performing a total pneumonectomy, careful dissection of the vessels and bronchus at the hilum with individual ligation of the former is the procedure of choice. This enables a higher division of the primary bronchus and an adequate exposure for removal of mediastinal lymph nodes. Thus, by resection of an adequate amount of the tumor-bearing tissue at its primary site and the regional lymph nodes which are the first to be involved by metastases, a much higher percentage of permanent cures may be expected.

\*Patient reported is living and well four and one-half years following operation.

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gives visibility for the division of adhesions in the anterior and superior aspects of the pleural space which are apt to be present in the case of carcinoma of the upper and middle lobes. This approach has been used for many years by Graham and T. Edwards and others for the removal of anterior mediastinal tumors, and if the incision lies beneath the breast in women, it may leave little evidence of scar following healing and little or no deformity visible on x-ray examination.

The posterolateral approach is made through an incision along the course of the seventh rib from its angle posteriorly to the anterior axillary line and may include the resection of a long segment of this rib subperiosteally with or without the division of the fourth, fifth, sixth, and eighth ribs posteriorly. This approach is used more especially for

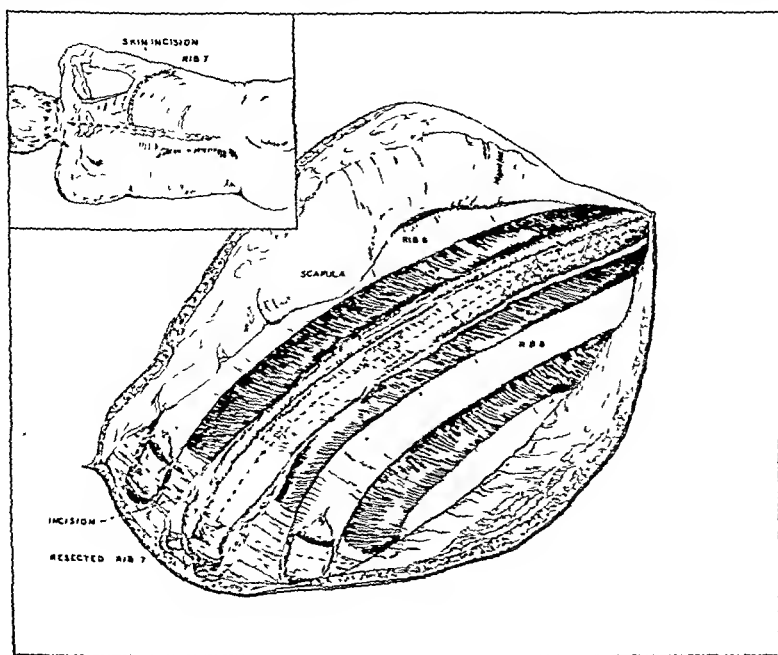


Fig. 9.—The posterolateral approach. The incision is made along the course of the seventh rib, extending upward near the spine posteriorly. The pleural space is entered through the seventh rib bed. Small segments of the sixth and eighth ribs posteriorly have been removed.

lobectomy, rather than for pneumonectomy, and has the advantage of permitting better visibility for the division of adhesions posteriorly and inferiorly between the lower lung lobe and the diaphragm. Since infection subsequent to obstruction of the bronchial tree by the tumor is present in a high percentage of cases, pneumonitis and bronchiectasis with subsequent inflammatory reaction between visceral and parietal pleurae with the production of adhesions are common complications. The disadvantage of this approach for pneumonectomy lies in an inadequate exposure of the anterior aspect of the hilum, a factor of great importance in the dissection of the hilar structures in the resection of the lung.

That there remains an indication for lobectomy in the treatment of a small percentage of slow-growing bronchogenic carcinomas is a view held by a number of authors.<sup>42</sup> This group of tumors originates in the primary stem bronchi, and they are very slow to invade adjacent structures or to metastasize. Since the risk of pneumonectomy still remains considerably higher than that of lobectomy, if the latter operation is adequate to remove all tumor-bearing tissue, it is thought to be the procedure of choice in these patients.

*Approach.*—Three main sites for approaching these operations have received considerable attention; namely, anterolateral, posterolateral, and lateral. The anterolateral approach which enters the pleural space

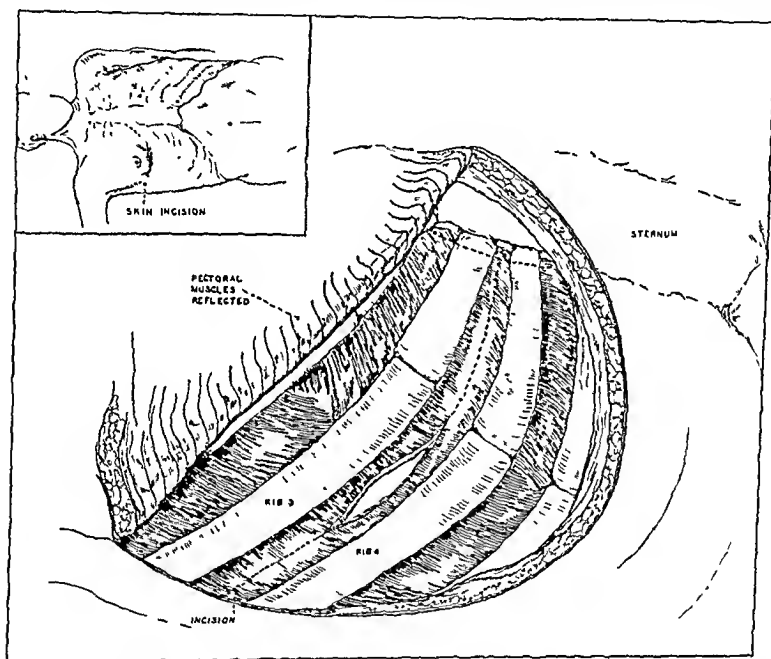


Fig. 8.—The anterolateral approach, showing the line of incision beneath the breast. With the pectoral muscles divided and elevated upward the pleural space is entered through the third intercostal space. The third and fourth costal cartilages may be divided near the sternum.

through the third or fourth interspace from the lateral border of the sternum to the postaxillary line received earlier attention for total pneumonectomy. The incision may be made either along the crease beneath the breast (especially in women) or just over the nipple along the line of the interspace, and the procedure may or may not include the division of the second, third, fourth, and fifth costal cartilages. Graham<sup>71</sup> and Overholt<sup>72</sup> have been strong advocates of this latter procedure; whereas, Richhoff<sup>73</sup> approaches through the third interspace without the division of ribs or cartilages. The anterolateral approach is especially applicable for pneumonectomy because of its adequate exposure of the anterior aspect of the hilum for a detailed dissection of its structures. It also

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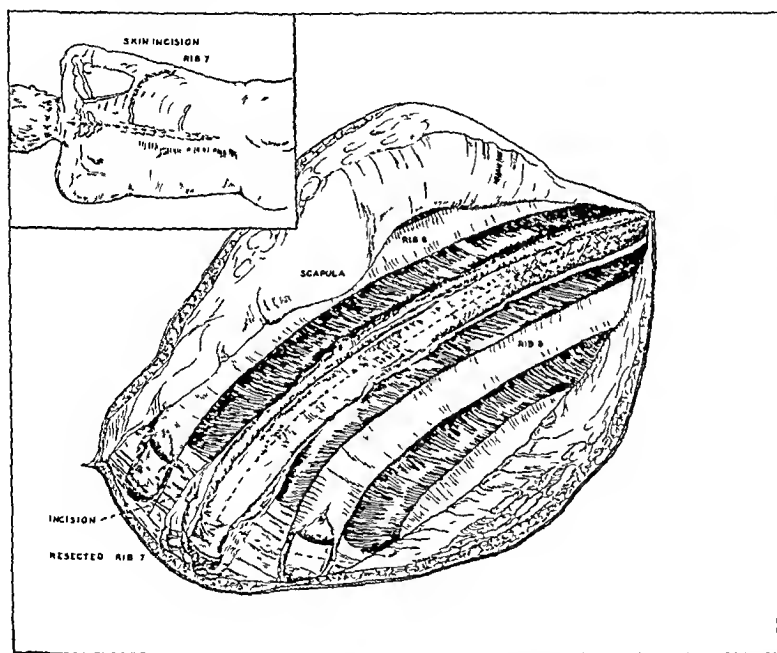


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More recently, a lateral approach has been devised and utilized by Crafoord,<sup>74</sup> of Stockholm, and at the present time is receiving ever-increasing favor in other parts of the world. This approach utilizes an incision along the course of the fifth rib, extending from the fourth rib at its angle posteriorly, downward and forward to the costochondral junction of the fifth anteriorly and dipping beneath the scapula on its way forward. After division of the muscles of the chest wall and elevation of the scapula almost the entire length of the fifth rib is removed subperiosteally. This approach combines all of the advantages of the two former approaches, thus the explanation for its increasing favor. It allows for more adequate exploration under direct vision and facilitates materially the removal of the involved structures.

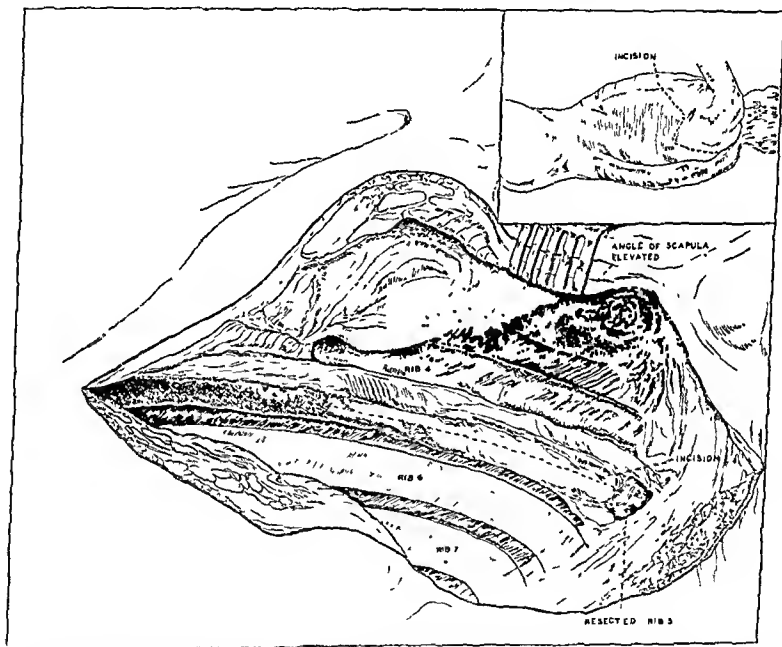


Fig. 10A.—The lateral approach. Insert shows the skin incision over the course of the fifth rib anteriorly and curving beneath the scapula posteriorly. After elevation of the scapula most of the fifth rib is resected and the pleural space entered through this rib bed.

Before making the incision for entering the chest, intravenous saline administration is begun and continued at a slow rate throughout the operation. If exploration reveals the tumor to be operable, blood for transfusion is substituted for the saline solution and administered at a slow rate during the lung resection. During the entire procedure, blood pressure and pulse recordings are made at five-minute intervals and the surgeon is informed if any severe alteration occurs.

On entering the pleural cavity, examination of the tumor is immediately carried out to ascertain operability. The degree of fixation to the mediastinum is of importance in determining this factor. Mediasti-

nal lymph nodes may be enlarged due to infection complicating the primary condition. Adhesions are divided and oozing of blood is controlled by direct application of warm, moist sponges. As previously mentioned, where adhesions are dense and extend over a wide area, shock may be so severe as the result of their separation that the two-stage operation is indicated. This consists of the mobilization of the pulmonary artery and its division between ligatures. The wound is then closed and the lung removed at a second stage. Where few dense adhesions are present and little shock is observed in their division, the one-stage operation is advisable and proceeds as follows: The diaphragm on the involved side is paralyzed by the division of the phrenic



Fig. 10B.—Photograph of patient showing healed incision of the lateral approach to the pleural cavity.

nerve between ligatures. This reduces the amount of motion in the lung to be removed and helps to reduce the residual space subsequent to surgery. Careful dissection of the hilar structures with mobilization of the main pulmonary artery and two pulmonary veins necessitates entering the mediastinal region, since that portion of the vessels lying outside of the mediastinum is too short for adequate ligation before division. Ligation of the vessels is best performed with nonabsorbable silk or linen sutures, rather than catgut, since the latter is more apt to slip, resulting in a fatal hemorrhage. The vessels are then divided

between ligatures, two of which have been placed proximal and one distal to the site of division. To insure permanent closure of the vessels a transfixion suture may be used for one of the two proximal ligatures. The mediastinum is then explored and all lymph nodes removed.

*Reflex Effects During Operation.*—Considerable emphasis has been placed by some authors on the deleterious effects during the dissection of the hilar structures, clamping of the bronchus, and ligation of the pulmonary artery due to reflex activity. It is well recognized that serious cardiorespiratory disturbances may result from reflex action due to stimulation of nerve endings in the parietal pleura, at the root of the lung, and in the mediastinum. The nerves over which these impulses must pass include the vagus, sympathetic, phrenic, and intercostal. This reflex action may be abolished by local anesthesia and may be increased by light general anesthesia. Morrison<sup>77</sup> produced sudden death in rabbits by crushing the pedicle with a clamp which produced an arrest of respiration in the inspiratory phase. This action could be prevented by first sectioning or injecting the vagus nerve proximally with novocain. Cardiac arrest was also produced by Nissin<sup>78</sup> and by O'Shaughnessy<sup>63, 79</sup> by clamping or ligating the hilum en masse in experimental animals. Dissection of the hilum may occasionally cause a slowing of the heart rate and lowering of the systemic blood pressure, the degree of which is of little consequence.<sup>16</sup> Temporary cardiac arrest has been reported due to this procedure, and pneumonectomy was prevented in one case when cardiac arrest resulted on attempts to clamp the pulmonary artery.<sup>55</sup> This is unusual, however, little change in blood pressure level or heart rate being the common observation. Animal experimentation carried out in monkeys and dogs by Monod<sup>76</sup> bears out the above clinical observations. Although inhibitory effects were noted, they were never sufficiently strong to produce cardiac arrest even with rough handling of the lung root or crushing the hilum en masse including the vagus nerve. Cocaine applied to the hilum before dissection has been advocated to avoid these reactions. I have never observed these untoward effects and from personal communications have been led to believe that they have been overemphasized.

*Closure of Bronchial Stump.*—Following the division of the pulmonary artery and veins, the primary bronchus is freed from the surrounding structures to a point not more than 2 cm. below the bifurcation of the trachea. The point of division of the bronchus will depend chiefly on the site of the tumor, a fact determined by bronchoscopy prior to operation. Cases have been reported in which even the lower part of the trachea has been resected for extremely high-lying tumors. Several methods for managing the bronchial stump have been advocated, but none has proved successful in 100 per cent of the cases. Leakage following closure of the stump has been one of the major causes of serious

postoperative complications. These complications include empyema, tension pneumothorax, pneumonia in the remaining lung, and sudden drowning of the remaining lung by fluid collected in the residual pleural space. These complications have given rise to the oft-repeated but as yet unanswered question as to whether thoracoplasty should be performed at the time of or following the pneumonectomy.

It was well established at an earlier date by Bettman,<sup>24</sup> and later substantiated in this laboratory,<sup>25</sup> that the healing power of the bronchus per se was peculiar in nature; thus when the bronchus was occluded by mass ligature following resection of an entire lung, reopening of the same could be predicted in a high percentage of animals. The explanation of this complication was chiefly on the basis of lack of healing in the bronchus per se when the lining mucosa remained intact. When the mucosa was destroyed by crushing of the bronchus or by cauterization prior to its obliteration by ligature or suture, reopening could be prevented in a high percentage of cases. Division of the bronchus in a biased direction and utilization of the musculo-fibrous portion for covering the end of the cartilaginous portion has been advocated by Rienhoff<sup>26</sup> as an additional safeguard against reopening. In young individuals, after closing the end of the bronchial stump by a row of interrupted sutures, inversion of the stump, as in treating the stump of an appendix, may be brought about by a series of interrupted mattress sutures. In older individuals, however, where the cartilages have become quite rigid, this is not possible. A more substantial closure in these cases must be obtained by the use of mattress sutures placed above the line of interrupted sutures closing the end of the bronchus as advocated by Overholt and others. Destruction of the bronchial mucosa by chemical cauterization has the advantage that raw surfaces of the bronchus are approximated by the mattress sutures and should give rise to more rapid solid healing. In closing the bronchial stump care should be taken not to disturb the bronchial artery since that portion of the bronchus distal to ligature or mattress sutures is partly nourished by this means. Following closure of the bronchus, burying the same in the mediastinum or covering it with a free lung parenchymal graft, as advocated by Churchill, may further enhance solid healing without subsequent reopening. This is a debated question, however, some preferring to leave it protruding into the pleural space.<sup>27</sup> Clean drapes are now placed about the wound, a change of gloves is made and a clean set of instruments used for closure of the wound. Protection of the wound edges by moist lap sponges during surgery will encourage healing by primary intention. Closure is made in layers, using a double strand of No. 0 chromic catgut for periosteal sutures placed around the ribs above and below the incision and a continuous suture of No. 00 chromic catgut for the intercostal structures. The muscles are carefully approximated with interrupted sutures of the latter material and closure completed without

drainage. After closure is complete, a needle introduced into the pleural space is attached to a pneumothorax apparatus to determine the residual pressures. Air is then aspirated until the pressures become within normal limits; i.e., minus 8 to 10 cm. of water. T. Edwards and Harrington have advocated drainage of this space following surgery for the removal of accumulated fluid and maintenance of pressure relationships. The drain is removed twenty-four to seventy-two hours later in order to avoid infection of the residual pleural space.

*Postoperative Care.*—The amount of blood lost during surgery and the degree of shock at the end of surgery determine whether a second blood transfusion is indicated. A higher percentage of successful results will be obtained where the free use of blood transfusions is employed when indicated. After the return of the patient to his room, oxygen is administered by a nasal catheter or by tent. If given by nasal catheter at the rate of 10 to 12 liters per minute, the amount may be sufficient for most patients. In the presence of a humid atmosphere or extreme elevation of temperature, oxygen given by the tent method is advisable. By either method, oxygen administration will diminish the strain on the cardiorespiratory system and reduce very definitely the incidence of cardiac failure. An apparatus readily available for the administration by mask of oxygen under pressure is advisable for occasionally its immediate use may be necessary.

Some authors, notably Rienhoff, have advocated the Trendelenburg position in bed for twenty-four hours following operation, maintaining that this permits free bronchial and tracheal drainage with minimal effort to the patient. Other surgeons favor the semisitting posture in which position cough and expectoration are somewhat facilitated. In either case, change of position from one side to the other or to the back every two or three hours while the patient is awake during the first two or three days is indicated. This helps to prevent the development of pneumonia in the remaining lung and tends to aid circulation. Administration subcutaneously or intravenously of 2,000 to 3,000 c.c. of saline solution or glucose daily during the first two or three days is indicated. A sudden rise in temperature to 101 or 102° with a somewhat rapid fall may be expected for the first two or three days. Some of this elevation is due to the absorption of blood from the pleural cavity and may persist for one or two weeks.

Examination of the chest by fluoroscopy or x-ray every two or three days is indicated in order to determine the condition of the residual pleural space and of the remaining lung as well as the position of the mediastinum. It is usually unwise to remove air or fluid from the residual pleural space to the point of creating high negative pressures. The air persisting there is gradually absorbed and replaced by fluid of a serosanguineous nature. When the pleural space is not prepared by the



use of beef broth prior to operation, the fluid found at this site following operation remains in a fluid state for at least several weeks or months following surgery.

Where healing of the wound occurs by primary intention, the patient may be able to sit out of bed by the end of two to three weeks and may be discharged from the hospital by the end of three or four weeks. If a

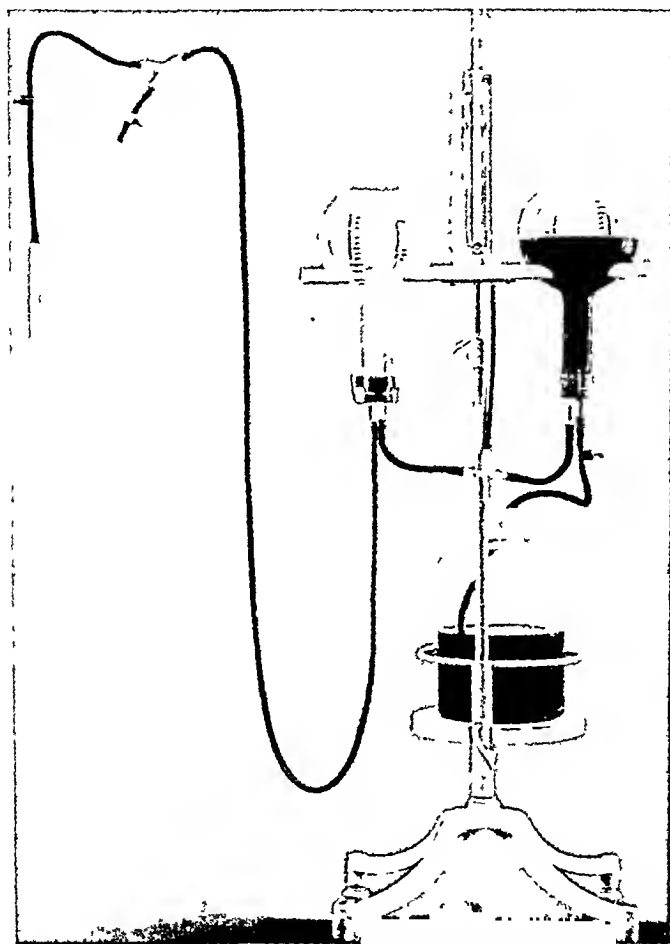


Fig. 11 —Modified double Wangensteen portable suction apparatus found to be satisfactory for draining and obliterating the pleural space following intrathoracic operations. A manometer connected with the tubing between the two upper flasks aids in determining the amount of suction applied to the pleural cavity.

cough develops or is persistent after operation, reopening of the bronchial stump with the production of a bronchial fistula must be suspected and is determined by bronchoscopic examination. In this event, an empyema of the residual pleural space must be expected and necessitates drainage of this space. Complete healing of the empyema may occur following adequate drainage with or without subsequent obliteration of the space by thoracoplasty.<sup>16</sup>

## READJUSTMENTS FOLLOWING PNEUMONECTOMY

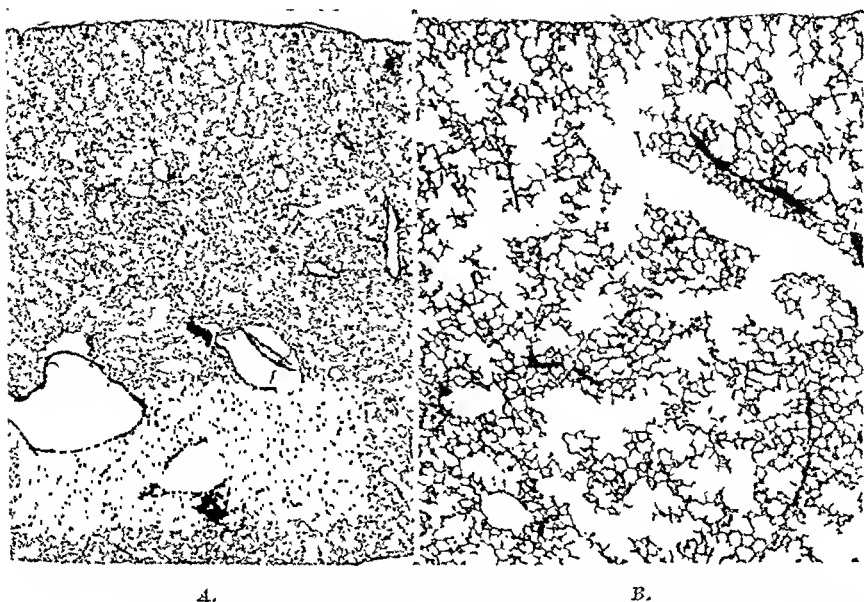
During the past eight years sufficient clinical material has been observed upon which definite conclusions can be based regarding the physical and physiologic alterations following pneumonectomy. Some of these may be observed within the first few hours after operation; viz., reduced respiratory movement on the side of surgery, with narrowing of the intercostal spaces, elevation of the diaphragm, and shifting of the mediastinum toward that side. These changes increase in degree during the subsequent few months and in addition there is a sinking of the pleural apex and a mild degree of scoliosis with the concavity toward the side on which the operation was made.

*Residual Pleural Space.*—Following the removal of an entire lung on one side the pleural space fills with a serosanguineous transudate and the air is gradually absorbed. It is usually unnecessary to remove air or fluid from this space following surgery provided a normal negative pressure is established after closure of the wound. As stated, some surgeons (Edwards,<sup>16</sup> Harrington<sup>81</sup>) prefer to drain this space for twenty-four to seventy-two hours in order to maintain a negative pressure. Rienhoff<sup>82, 84</sup> reports that the accumulating fluid coagulates within a few days, with the formation of many pockets in the meshes of a fibrous tissue network. In our experience this fluid remains uncoagulated for weeks or months<sup>85</sup> and becomes serofibrinous in character. The space is markedly reduced in size by elevation of the diaphragm, some shift of the mediastinum, contraction of the chest wall, and thickening of the parietal pleura. An autopsy performed on a 58-year-old man who died of general peritonitis nine months after total left pneumonectomy revealed 125 c.c. of serofibrinous exudate occupying a cone-shaped space made by a contracted parietal pleura which varied from 0.5 to 2 cm. in thickness.<sup>85</sup> The discrepancy between these findings and those of Rienhoff's report may well be explained by the preoperative preparation in his patients with beef broth which stimulates granulation tissue production.

In children, the mediastinum is able to shift more easily than in adults. Thus the lung on the uninvolved side actually herniates into and diminishes the size of the residual pleural space. This is also true in dogs and in addition little or no pleural fluid or parietal pleural thickening is found following pneumonectomy.<sup>86</sup>

That the accumulation of fluid in the residual pleural space constitutes a real hazard is emphasized by the report of sudden death from asphyxia due to flooding of the remaining lung by sudden opening of the bronchial stump.<sup>87</sup> This is one factor that has given rise to the frequently debated but as yet unanswered question as to whether a thoracoplasty to obliterate this space should not accompany or follow the pneumonectomy.

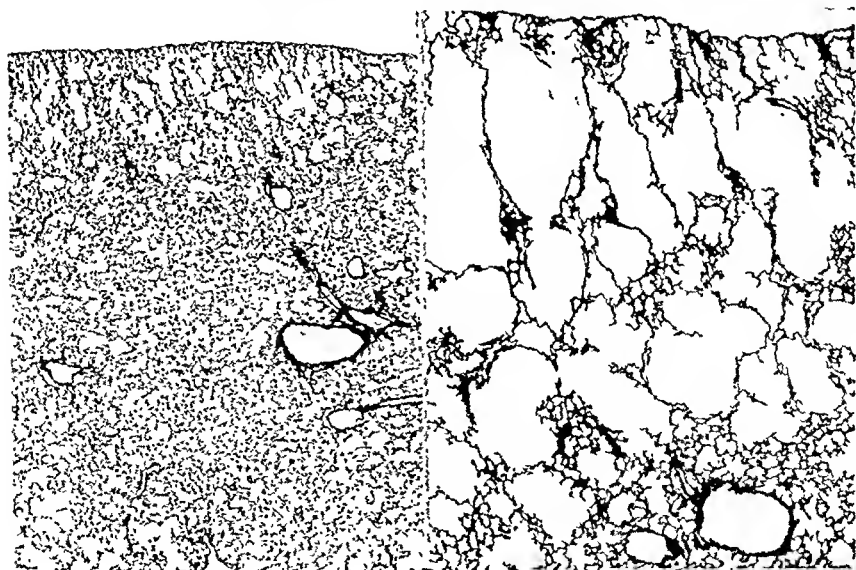
*The Remaining Lung.*—Due mainly to the shift of the mediastinum and also to some extent to lowering of the diaphragm on the unin-



A.

B.

Fig. 12.—Microscopic appearance of the lung following reduction of lung function to three lobes (38.7 per cent). Note uniform dilatation of the terminal respiratory units with no evidence of emphysema. (A.  $\times 7$ . B.  $\times 20$ .)



A.

B.

Fig. 13.—Microscopic appearance of the remaining one upper lobe following the resection or collapse of the other five lobes (lung function remaining approximately 15 per cent). Note marked dilatation of the terminal respiratory units more especially near the surface of the pulmonary tissue. In some places emphysematous changes are demonstrable. (A.  $\times 7$ . B.  $\times 20$ .)

Complete report of case shown in Figs. 6 A-D to appear in SURGERY.

volved side,<sup>84</sup> the remaining lung fills a larger space following total pneumonectomy. Whether there is actual hypertrophy, hyperplasia, or true emphysematous changes has been a controversial subject. Rienhoff believes that neither of these occurs but that there is a simple overdistention of the pulmonary tissue, a view shared by most authors. This change is more marked following removal of the left lung since the right lung herniates into the left pleural space more easily than contrariwise. This is thought to be due chiefly to the anatomical arrangement of the mediastinal structures. Rienhoff has found similar alterations in both children and adults varying only in the degree of severity.

Considerable animal experimentation regarding the reduction of lung function has resulted in the following conclusions: If no more than one lung is removed in dogs and cats, only compensatory overdistention with no production of true emphysema of the lung occurs (Rienhoff, Reichert, and Heuer<sup>88</sup>). In rabbits some areas showed changes analogous to compensatory emphysema following total pneumonectomy (Morrison<sup>77</sup>). In rats (Hibber<sup>89</sup>) and in young cats (Longacre and Johausmann<sup>90</sup>) actual hyperplasia occurs following pneumonectomy. Behrend and Mann<sup>91</sup> however, believe the increased volume of the remaining lung is chiefly due to the use of functional units which are ordinarily inactive. Due to the extreme elasticity of lung tissue, Phillips and his associates<sup>86</sup> and Rasmussen and his co-workers<sup>92</sup> of this laboratory found it impossible to produce true emphysema until only one upper lobe or about 15 per cent of the lung tissue was functioning. The lobes revealed marked dilatation of the terminal respiratory units including the alveoli, air sacs, atria, and alveolar ducts, the overdistention being especially marked in the latter. There was some fragmentation of the walls of the alveolar ducts, but the alveoli for the most part were intact, with no destruction of elastic tissue and little disturbance of capillaries of pulmonary circulation. This latter is substantiated amply by both clinical and experimental evidence.

*Cardiorespiratory Reserve.*—Following pneumonectomy little or no cardiorespiratory embarrassment while at rest or under mild exercise occurs in an otherwise normal individual. The first patient to survive total pneumonectomy for carcinoma (performed by Graham), a doctor, is living and without symptoms more than eight years after surgery. He continues his surgical practice and during ordinary activities is unaware of signs or symptoms of embarrassment referable to the cardiorespiratory system. Many like examples of a shorter duration show this to be the rule rather than the exception. Much light has been shed on this aspect of the subject by animal experimentation. As early as 1922 Heuer and Andrus<sup>93</sup> observed a temporary rise in alveolar carbon dioxide and a fall in alveolar oxygen following pneumonectomy in dogs. With these changes there was an associated temporary rise in carbon-dioxide content and capacity of the blood with a marked

fall in the oxygen content and a marked decrease in the oxygen saturation. With this Andrus<sup>94</sup> found an increase of 40 per cent in blood flow through the opposite lung within a few hours after pneumonectomy. In other studies<sup>95</sup> he demonstrated an increase in respiratory volume, pulse rate, hemoglobin, and red cell count within twenty-four hours after ligation of the left main bronchus. All of the above alterations excepting the hemoglobin and oxygen capacity returned to normal within approximately one month.

Cardiorespiratory reserve following pneumonectomy was further studied by Longacre, Carter, and Quill<sup>96</sup> using induced exercises and anoxemic tests on young dogs before and at various periods following surgery. They found it to be sufficient to tolerate moderate exercise. According to their methods the reserve was reduced to 50 per cent by total pneumonectomy, but after four months this was raised to 66 per cent. The mechanism for this compensation could not be adequately explained.

TABLE I

RESULTS OF TEST FOR RESPIRATORY RESERVE AT REST IN NORMAL, 3-LOBE, 2-LOBE AND 1-LOBE DOGS BY REDUCTION OF ATMOSPHERIC PRESSURE IN EVACUATION CHAMBER (RESERVE OF 3-LOBE DOGS WAS SAME AS THAT FOR NORMAL ANIMALS WHILE THAT OF 1- AND 2-LOBE DOGS WAS SOMEWHAT REDUCED)\*

STANDARD ATMOSPHERIC PRESSURE		CONDITION OF ANIMAL AND % OF FUNCTIONING LUNG	NO. OF DOG	ALTITUDE TOLERATED	TIME OF ASCENT (MIN.)	AVERAGES	
ALTITUDE (FT.)	PRESSURE (MM. HG)					ALTITUDE (FT.)	PRESSURE (MM. HG)
0	760	Normal (6 lobes) 100%	1	30,500	10	30,400	221.6
1,000	733		2	30,500	10		
5,000	632.4		3	29,500	10		
10,000	522.6		4	32,000	8		
15,000	428.8		4	29,500	11		
20,000	349.2	3 lobes 38%	917	32,000	6	30,000	225.6
25,000	282		993	32,000	7		
30,000	225.6		3	25,000	7		
35,000	178.7		637	31,000	9		
40,000	140.7		871	30,000	9		
		2 lobes 23%	636	27,500	4	26,000	269.8
			869	24,500	6		
		1 lobe 15%	635	26,500†	5	25,833	272
			621	25,000†	6		
			695	26,000	10		

\*From Rasmussen, R. A., Adams, W. E., and Hrdina, L. S.: SURGERY 10: 85, 1941.

†Failed to recover.

‡Did not become unconscious.

The above findings are in agreement with data more recently accumulated in our laboratory.<sup>86, 92</sup> A more severe strain was placed on the cardiorespiratory function by reducing the lung function to as little as one upper lobe or approximately 15 per cent of normal. Studies of the blood revealed findings similar to those of Andrus and Heuer. A second series of dogs was subjected to extremely rarefied atmospheres by placing them in a chamber in which the pressure could be reduced. Normal dogs when subjected to this procedure were able to

tolerate a reduction in pressure to approximately 221.6 mm. Hg (altitude of 30,400 feet) or a pressure similar to that tolerated by man<sup>97</sup> before becoming unconscious. The same results were obtained when dogs with three lung lobes functioning (both upper lobes and the right middle, or about 38 per cent of normal) were subjected to the test. When one-lobe dogs were subjected to the procedure they became unconscious at 272 mm. Hg pressure (altitude 25,833 feet), thus showing a high reserve in spite of the fact that little lung tissue was functioning. Dogs with one lung lobe functioning have been observed for more than three years and appear to be better compensated at the end of that time than immediately or a few weeks after surgery.

#### RESULTS OF SURGICAL TREATMENT DURING THE PAST DECADE

An appraisal of the accomplishments of any surgical procedure by the use of statistical material is usually far from satisfactory. However, some information can be gained from reports of personal experiences or collected cases which have appeared in the literature. Thus a monograph by Crafoord in 1938 presented a detailed report on 12 pneumonectomies for carcinoma of the lung with 3 successful results. He discussed the cause of failure in the remaining patients and described the technique developed during this experience. In 1939 Ochsner and DeBakey<sup>47</sup> discussed the results in 7 personal and 76 collected cases by twenty-three authors reported since 1933. Of these, 32 had survived more than 2 months and 25 were living at the time of the report. In 1940 Overholt and Rumel<sup>98</sup> reported the results of a personal series of 17 pneumonectomies with 11 recoveries. Of these 8 were living and without evidence of recurrence or metastases up to as long as 6¼ years following operation.

In 1941 at the twenty-fourth annual meeting of the American Association for Thoracic Surgery this subject was thoroughly discussed and the following statistics were given: E. F. Bulter, 16 pneumectomies with 11 recoveries; E. A. Graham, 35 successful pneumonectomies with patients living without evidence of tumor at the present time: 1 for 8+ years, 1 for 6+ years, 2 for 5+ years, 11 for 3+ years, and 20 for more than 1½ years; his mortality for the past 18 months (20 cases) was 25 per cent; prior to this it had at one time been as low as 12.5 per cent; S. W. Harrington, 9 pneumonectomies with 6 recoveries; R. H. Overholt, 28 pneumonectomies with 20 recoveries during the past 8 years; the mortality rate which was 44 per cent during the first 3 years dropped to 21 per cent during the last 5 years; W. E. Rienhoff, Jr., 52 pneumonectomies with a mortality of 25 per cent during the past 8 years; N. S. Shenstone reported the results in 13 pneumonectomies; prior to January, 1938, there were 4 operations with 2 recoveries; since that date there have been 9 operations with 7 recoveries; at the University of Chicago Clinics there have been 6 pneumonectomies with 3 recoveries, the longest living and well over 4½ years.

These statistics represent only a fraction of the total number of successful cases obtained both in America and abroad and are intended only to emphasize what has been accomplished by a small group of surgeons. The mortality rate per se is not prohibitive and to a great extent depends on the choice of patients for surgery, and the surgeon's specialized training in the management of diseases of the thorax. Of great importance is the gradually increasing number of survivals of more than five years, the longest being over eight years.

It is thus very obvious that real progress has been made in the surgical management of carcinoma of the lung. However, it is only the beginning, and one of the main hazards to its continued advancement, as pointed out by Graham, is the development of a pessimistic attitude among those qualified for and actively engaged in the treatment of these patients. Statistical results in pioneer work on a previously hopeless problem are bound to be discouraging. However, when one considers that all accomplishments have been made within one decade, it compares very favorably with the treatment of malignant disease elsewhere in the body. Undoubtedly continued improvement can and will be achieved. Earlier diagnoses and correlation of the pathologic picture with its clinical significance will be a big step in this direction.

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## Book Reviews

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**Infantile Paralysis: Anterior Poliomyelitis.** By Philip Lewin, M.D., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor Orthopedic Surgery, Cook County Graduate School of Medicine; Attending Orthopedic Surgeon, Cook County and Michael Reese Hospitals; Consulting Orthopedic Surgeon, Municipal Contagious Disease Hospital, Chicago. Cloth. Pp. 372, with 165 illustrations. Philadelphia, 1941, W. B. Saunders Co. \$6.

The author has produced a volume on the subject of poliomyelitis which should be widely used as a handbook and guide both for physicians who may be especially interested in the diagnosis and treatment of the disease and for the general practitioner whose interest may be only casual and occasional. It covers the subject from the standpoint of etiology, resistance and immunity, epidemiology, pathology, symptomatology and treatment, both during the immediate convalescent stage and the stages of late convalescence and operative treatment.

The author has borrowed freely from the writings of others and in fact has included in the material sections by numerous authors of prominence whose experience gives authority to their portion of the text.

The arrangement of this book seems excellent to the reviewer. It is adequately and well illustrated. It is not too large and the chapters are not too long so that it should be a useful textbook and handbook for those interested in this disease.

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**Infantile Paralysis: A Symposium Delivered at Vanderbilt University, April, 1941.** Cloth. Pp. 293, with 47 illustrations. New York, 1941, The National Foundation for Infantile Paralysis, Inc.

Recent advances in our knowledge of infantile paralysis are due in large measure to the liberal aid which the National Foundation for Infantile Paralysis has given to various groups of workers. The present volume, representing another activity sponsored by the Foundation, constitutes six lectures delivered at Vanderbilt University by outstanding authorities in the field. Each of the lectures makes up a chapter. Chapter I is on the "History of Poliomyelitis Up to the Present Time," by Professor P. F. Clark of the University of Wisconsin Medical School. Chapter II is by Dr. Charles Armstrong, Senior Surgeon, United States Public Health Service, on "The Etiology of Poliomyelitis." Chapter III on the "Immunological and Serological Phenomena in Poliomyelitis" is by Dr. T. M. Rivers, Director, the Hospital of the Rockefeller Institute for Medical Research. "The Pathology and Pathogenesis of Poliomyelitis" forms Chapter IV, and is written by Dr. E. W. Goodpasture of Vanderbilt University School of Medicine. Chapter V is a discussion of "The Epidemiology of Poliomyelitis," by Dr. J. R. Paul of Yale University School of Medicine. The final chapter is by Dr. F. R. Ober of Harvard University on "Treatment and Rehabilitation of the Poliomyelitis Patient."

Each of the chapters is well documented. The bibliography is placed at the end of the last lecture and numbers 575 references. The subject is presented in a

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lucid and scholarly manner. There is considerable overlapping of material in some of the lectures which could have been obviated by more careful editing. This repetition may have served the lecturers well, but it dulls the readers' interest. The volume is well indexed.

The contents of the volume are authoritative and the monograph is highly recommended to anyone desiring a comprehensive statement concerning the present-day problem of infantile paralysis. The National Foundation for Infantile Paralysis, Inc., is to be commended for undertaking such a project.

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### Erratum

On page 687 of the October, 1941, issue in the "Report of the Meeting of the American Association for Thoracic Surgery, June 9-11, 1941, Toronto, Ontario" by John R. Paine, M.D., Minneapolis, Minn., reference is made to the Ross-Lambert Prize Essay read by C. A. Moyer, Boston. The award should appear as the Rose Lampert Graff Foundation Prize Essay.

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